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ALIVER

The ALIVER Consortium has developed and optimized a novel ‘liver dialysis device’ – DIALIVE

Overview of ALIVER:

+ Consortium comprised of experts in liver failure, hospitals, SMEs, not-for-profit organisations

+ Funded from EU Horizon 2020 research and innovation programme

+ Benefits from 25 years of experimental research and data collection on extracorporeal perfusion as a therapy option in liver failure

For more info, visit www.aliver.info

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733057.

JOURNAL OF HEPATOLOGY

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Abstracts of The Digital International Liver Congress™ 2020
August 27–29, 2020

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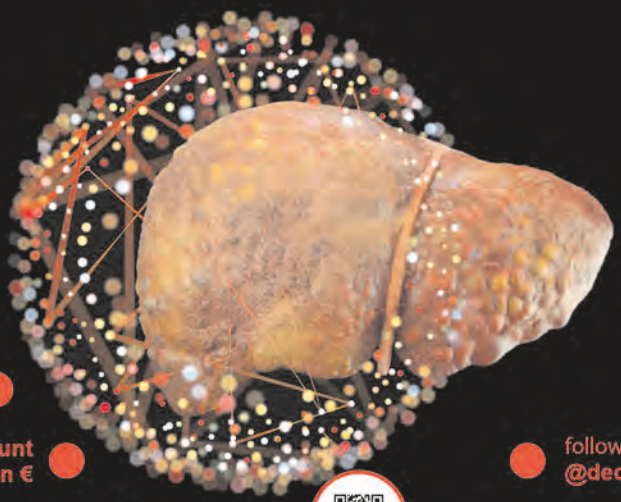
DECISION



project duration
5 ½ years

10 countries
21 institutions

grant amount
6 million €

kick-off
1st April 2020

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The objective of the DECISION project is to enhance the understanding of the pathophysiology of decompensation of cirrhosis leading to acute-on-chronic liver failure (ACLF) or death. This consortium will take advantage of already existing large and clinically well characterized cohorts to ultimately develop prognostic and response tests and combinatorial therapies tailored to the needs of individual patients to decrease the risk of short-term death.

- Systems level elucidation of the pathophysiology of acute decompensation of cirrhosis at multiple levels (genetic, epigenetic, transcriptomic, metabolomics, lipidomics, miR, and extracellular vesicles)
- Integration of existing clinical data and new multi-omics data from 2,200 patients with more than 8,600 measurements
- Development of new combinatorial therapies
- Optimization of therapies using existing and newly developed animal models
- Development of new tests for prediction of outcome and response to new therapies
- Phase II clinical trial to test new combination therapies
- Creation of new guidelines for prediction and treatment of acute decompensation of cirrhosis to prevent ACLF and death

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 847949.

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Registration of Clinical Trials
The *Journal of Hepatology* endorses the policy of the WHO and the International Committee of Medical Journal Editors (ICMJE) on the registration of clinical trials. Therefore, any trial that starts recruiting on or after July 1, 2005 should be registered in a publicly owned, publicly accessible registry and should satisfy a minimal standard dataset. Trials that started recruiting before that date will be considered for publication if registered before September 13, 2005.
More detailed information regarding clinical trials and registration can be found in New Engl J Med 2004; 351:1250–1251 and New Engl J Med 2005; 352:2437–2438.

LITMUS

The overarching aim of LITMUS is to develop, robustly validate and advance towards regulatory qualification biomarkers that diagnose, risk stratify and/or monitor NAFLD/NASH progression and fibrosis stage.

Discover more on litmus-project.eu

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No. 777377. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. IMI.

LIVER SCREEN

Screening for liver fibrosis population-based study across European Countries

A project that will change the paradigm of diagnosis of chronic liver diseases

AIM:

To assess the prevalence of liver fibrosis in the general population using Transient Elastography, with the objective of establishing criteria for screening for liver fibrosis in the population.

An Horizon 2020 funded project - Grant Number 847989

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General session I and opening ceremony

GS01

Bezafibrate add-on therapy improves liver transplantation-free survival in patients with primary biliary cholangitis: a Japanese nationwide cohort study

Atsushi Tanaka[1], Junko Hirohara[2], Toshinari Nakano[2], Kosuke Matsumoto[1], Olivier Chazouillères[3], Hajime Takikawa[4], Bettina Hansen[5], Fabrice Carrat[6], Christophe Corpechot[3]. [1]*Teikyo University School of Medicine, Medicine, Tokyo, Japan;* [2]*Kansai Medical University, The Third Department of Internal Medicine, Hirakata, Japan;* [3]*Sorbonne University, Reference Center for Inflammatory Biliary Diseases and Autoimmune Hepatitis, Saint-Antoine Hospital, APHP, Paris, France;* [4]*Teikyo University School of Medicine, Medical Technology, Tokyo, Japan;* [5]*University Health Network & IHPME, University of Toronto, Toronto Centre for Liver Disease, Toronto General Hospital, Toronto, Canada;* [6]*Sorbonne University, Pierre Louis Institute of Epidemiology and Public Health, Paris, France*
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Background and Aims: Bezafibrate (BZF) is a dual PPARs/PXR agonist with potent anti-cholestatic efficacy. Beneficial effect of BZF on symptoms and biochemical features of primary biliary cholangitis (PBC) has been reported but its long-term efficacy on survival remains to be determined. In Japan BZF (400 mg/d) has been used as *de facto* second-line treatment for PBC patients with incomplete response to ursodeoxycholic acid (UDCA, 13–15 mg/d) since 2000's. Herein, we retrospectively investigated long-term efficacy of bezafibrate, taking advantage of a large-scale nationwide cohort of PBC patients in Japan.
Method: The Japanese PBC cohort is established by the nation-wide surveys, initiated in 1980 and updated every 3 years by the Intractable Hepato-Biliary Diseases Study Group (Japan PBC Study Group). To date, 9,919 patients with PBC have been registered. Primary and secondary outcomes (all-cause death or liver transplantation (LT); liver-related death or LT) were assessed using multivariable- or IPTW-adjusted Cox models with UDCA and BZF as time-varying covariates. Baseline covariates included age, sex, diagnosis year (by 10 years), presence of symptoms, serum levels of bilirubin, alkaline phosphatase, and albumin, and histological stage (early vs. advanced stage). Multiple imputation method was used for missing starting data of UDCA or BZF, and Cox models excluding missing data were used as sensitivity analysis.
Results: 1,739 patients were excluded from the analysis due to missing data in terms of outcome and final follow-up date. The remaining 8,180 patients were included: mean age at diagnosis 56.9yrs, 1,104 males (14%). Treatment protocol included UDCA monotherapy (6,087; 74%), a combination of UDCA and BZF (943; 12%), and no treatment (1,133; 14%). Exposure to BZF add-on therapy was associated with a significant improvement in long-term outcome as compared to UDCA alone or no treatment; Compared to no treatment, adjusted hazard ratio (aHR) for all-cause death or LT was 0.55 (95% CI 0.47–0.65, $p < 0.0001$) in patients treated with UDCA monotherapy, while BZF therapy conferred a further risk reduction of 0.23 (95% CI 0.15–0.35, $p < 0.0001$) when added to UDCA (Figure). Related HRs for liver-related death or LT were 0.52 (95% CI 0.43–0.63, $p < 0.0001$) and 0.21 (95% CI 0.12–0.37, $p < 0.0001$), respectively. Sensitivity analysis indicated similar significant improvement of survivals with BZF and UDCA combined therapy.

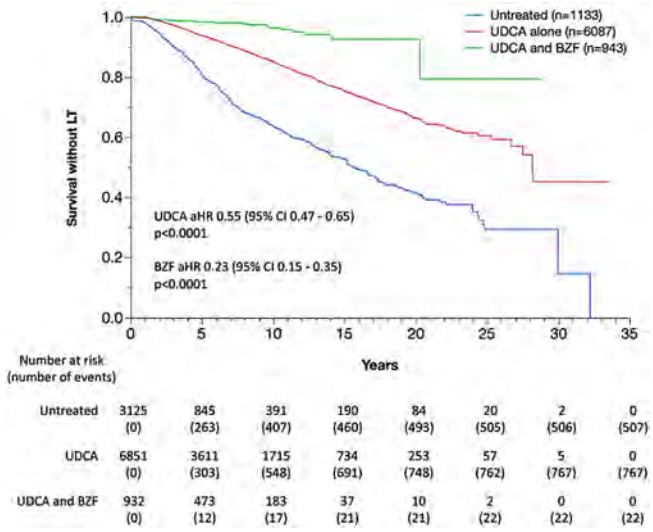

Figure: LT-free survival rates of Japanese patients with PBC according to time and treatment groups.

Conclusion: Combined treatment with BZF and UDCA in patients with PBC is associated with reduced risk for mortality or needs for LT as compared to UDCA alone.

GS02

Virulence-related genes in fecal metagenomes associated with mortality in patients with alcoholic hepatitis

Sonja Lang[1], Yi Duan[1,2], Yan Shao[3], Kevin Vervier[3], Peter Stärkel[4], Trevor Lawley[3], Bernd Schnabl[1,2]. [1]*Department of Medicine, University of California San Diego, La Jolla, CA, USA;* [2]*Department of Medicine, VA San Diego Healthcare System, San Diego, CA, USA;* [3]*Host-Microbiota Interactions Laboratory, Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton;* [4]*St. Luc University Hospital, Université Catholique de Louvain, Brussels, Belgium*
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Background and Aims: Intestinal dysbiosis is associated with the development and progression of alcohol-related liver disease (ALD), but most studies have focused on diversity, relative abundance and metabolic profiles of specific microorganisms. Bacterial virulence factors are proteins or peptides encoded by bacterial genes that help the organisms colonize the intestine or mediate disease. The aim of this study was to study the presence of virulence factors of the commensal gut microbiota in ALD and to correlate virulence factors with outcome in alcoholic hepatitis patients.
Method: Alcoholic hepatitis patients were enrolled at 9 centers in Europe, the United States, and Mexico in a multi-center observational

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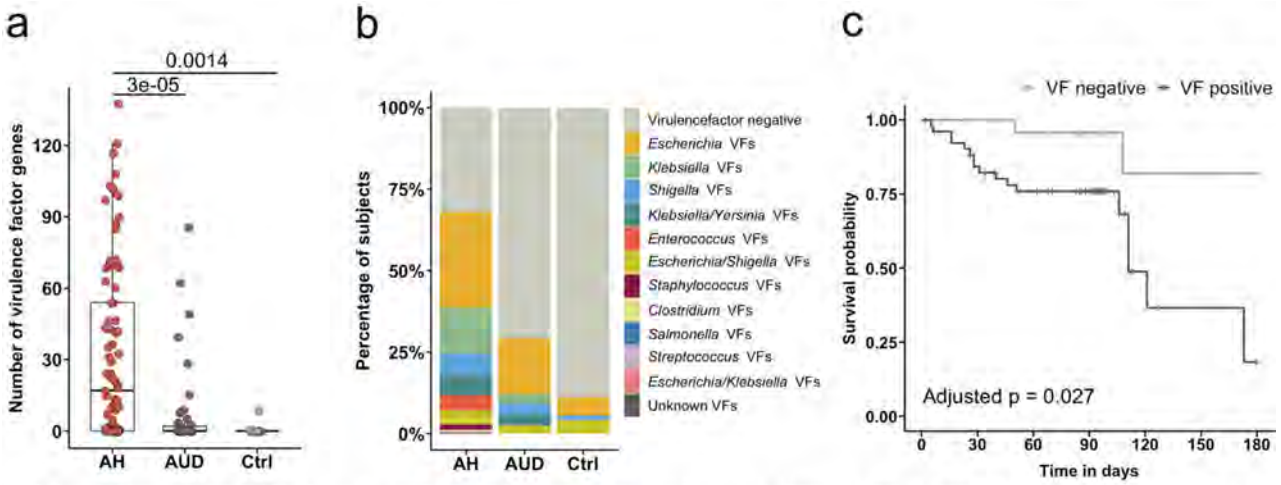

Figure legend: (a) Presence of 350 different virulence-related core genes in fecal samples from 81 patients with alcoholic hepatitis (AH), 41 patients with alcohol use disorder (AUD), and 9 controls (Ctrl). (b) Relative abundance of virulence factors found in fecal samples from 81 patients with alcoholic hepatitis, 41 patients with alcohol use disorder, and 9 non-alcoholic controls; factors are color-coded by genus of bacteria that produce them. (c) Kaplan-Meier curve of survival of patients with alcoholic hepatitis whose fecal samples were virulence factor (VF)-positive (n=55) or VF-negative (n=26). For the only patient who underwent liver transplantation, the transplantation date was considered as date of death. Patients were censored at the time point they were last seen alive.

Figure: (abstract: GS02)

study. We analyzed intestinal bacterial metagenomes and genes that encode virulence factors by using shotgun sequencing in fecal samples from 81 patients with alcoholic hepatitis, 41 patients with alcohol use disorder, and 9 non-alcoholic controls. The sequences were aligned with those in the virulence factor gene database (VFDB). Virulence factor associated genes were compared among the three groups. We further used multivariate Cox regression analysis to assess associations of virulence factors with 180-day mortality.

Results: The core virulence factor genes of the VFDB included 350 different, experimentally verified genes that encode virulence factors. Significantly more virulence factors were found in fecal metagenomes from patients with alcoholic hepatitis than patients with alcohol use disorder or controls (Fig. 1a). Overall, fecal samples from 68% of patients with alcoholic hepatitis expressed at least one virulence factor gene, compared with 29% of patients with alcohol use disorder and 11% of controls ($p < 0.001$). The most frequently observed virulence factors were derived from *Escherichia*, followed by *Klebsiella*, *Shigella, Klebsiella* or *Yersinia,* and then *Enterococcus* (Fig. 1b). 82% of virulence factor-negative alcoholic hepatitis patients were alive after 180 days following enrolment, compared with 18% of virulence factor-positive patients (hazard ratio adjusted for antibiotic and steroid treatment 5.32 (95% CI 1.20–23.50), $p = 0.027$, Fig. 1c).

Conclusion: The presence of virulence factors in the commensal gut microbiota determines mortality on patients with alcoholic hepatitis. Assessing the abundance of specific virulence factors might lead to new diagnostic biomarkers and treatment targets in patients with alcoholic hepatitis.

GS03

Liver involvement in patients with telomere-related genes mutations: prevalence, clinical, radiological, pathological features, outcome and risk factors

Sabrina Sidali[1], Raphaël Borie[2], Sicre Flore[3], Elodie Lainey[4], Pierre-Emmanuel Rautou[1], Jacques Cadranel[5], Jean-marc Naccache[5], Vincent Cottin[6], Jérôme Dumortier[7], Emmanuel Jacquemin[8], Nousbaum Jean Baptiste[9], Sandrine Hirschi[10], Arnaud Bourdin[11], Magdalena Meszaros[11], Sebastien Dharancy[12], Sophie Hilaire[13], Vincent Mallet[14], Reynaud-Gaubert Martine[15], Louis Terriou[12], Frédéric Gottrand[16], Wadih Abou Chahla[16], Jean Emmanuel Khan[17], Paul Carrier[18], Faouzi Saliba[19], Laura Rubbia-Brandt[20], Laure Elkrief[21], Victor de Lédinghen[22], Armand Abergel[23], Tournilhac Olivier[24], Yasmina Chouik[7], Antoine Coupier[7], Thierry Leblanc[4], Isabelle Ollivier-Hourmand[25], Eric Nguyen Khac[26], Hélène Morisse-Pradier[27], Kinan El Husseini[27], Odile Goria[28], Ba Ibrahima[29], Dominique Roulot[30], Christophe Bureau[31,32], Hilario Nunes[33], Dominique Valla[1], Valérie Paradis[34], Kannengiesser Caroline[29], Aurélie Plessier[1]. *[1]Hospital Beaujon AP-HP, Hepatology, Clichy, France; [2]Bichat-Claude Bernard Hospital, Pneumology, Paris, France; [3]Saint Louis Hospital, Hematology, Paris, France; [4]Hôpital Robert Debré, Hematologie, Paris, France; [5]Hospital Tenon Ap-Hp, Pneumologie, Paris, France; [6]Lyon Sud Hospital Center, Pneumology, Pierre-Bénite, France; [7]Hospital Édouard Herriot, Hepatology, Lyon, France; [8]Bicetre Hospital AP-HP, Pediatric Hepatology, Le Kremlin-Bicêtre, France; [9]Hospital Center Regional University Morvan De Brest, Hepatology, Brest, France; [10]Chu Strasbourg, Pneumology, Strasbourg, France; [11]Hospital Center University De Montpellier, Pneumology, Montpellier, France; [12]Chu De Lille, Hematology, Lille, France; [13]Hospital Foch, Hepatology, Suresnes, France; [14]Hospital Cochin, Hepatology, Paris, France; [15]Hôpital Nord, Pneumology, Marseille, France; [16]Chu De Lille, Pediatric Department, Lille, France; [17]Hospital Foch, Internal Medicine, Suresnes, France; [18]University Hospital Limoges Dupuytren Hospital, Hepatology, Limoges, France; [19]Hôpital Paul-Brousse Ap-Hp, Hepatology, Villejuif, France; [20]Hôpitaux Universitaires de Genève (HUG), Pathology, Genève, Switzerland; [21]Hôpitaux Universitaires de Genève (HUG), Hepatology, Genève, Switzerland; [22]Chu De Bordeaux - Haut-Lévêque, Hepatology, Pessac, France; [23]Centre Hospitalier Universitaire, Hepatology, Clermont-Ferrand, France; [24]Centre Hospitalier Universitaire, Hematology, Clermont-Ferrand, France; [25]Hospital Center University Of Caen Normandie, Hepatology, Caen, France; [26]Chu D'amiens-Picardie Site Sud, Hepatology, Amiens, France; [27]CHU Charles Nicolle, Pneumology, Rouen, France; [28]CHU Charles Nicolle, Hepatology, Rouen, France; [29]Bichat-Claude Bernard Hospital, Genetic Department, Paris, France; [30]Avicenne Hospital (AP-HP), Hepatology, Bobigny, France; [31]Hospital Purpan, Hepatology, Toulouse, France; [32]Hospital Purpan, Hepatology, Toulouse, France;*

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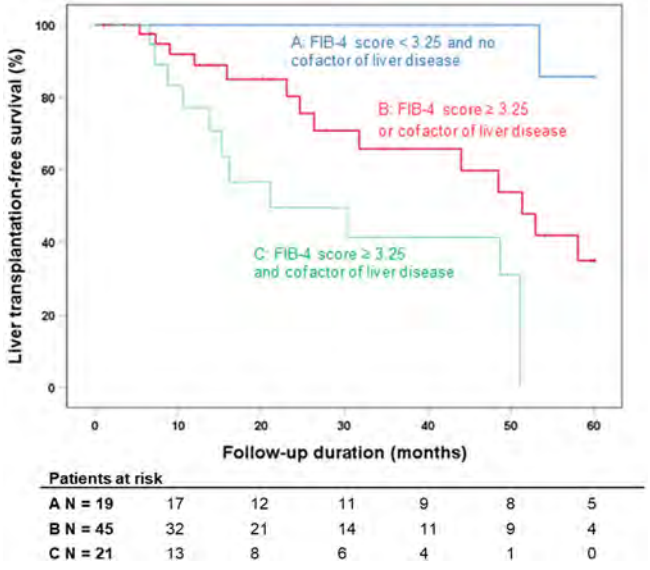
Background and Aims: Germline mutations of telomere-related genes (TRG) induce excessive shortening of telomeres, genetic instability and early cell aging. The aim of this study was to provide a detailed characterization of liver involvement (LI) associated with these rare mutations.
Method: Retrospective analysis of all patients in whom a pathogenic germline mutation of one or more TRG has been identified between 2004 and 2019, in 25 pneumology, haematology and hepatology French tertiary centers. LI was defined as serum transaminases (AST and/or ALT) >30 IU/L and/or abnormal liver morphology. Survival analysis (Kaplan-Meier method) was performed only in patients who had both diagnosis of LI and genetic mutation after 2004.
Results: 132 patients were included: 95 with LI; 94 men; median age 57 years (35–63); 77 with *TERT* mutation, 26 with *TERC* mutation, and 29 mutations in other genes; telomere length <1st percentile in 95% of the patients. Patients with LI had pulmonary, blood, skin, bone, ocular involvement in 82%, 77%, 55%, 39% and 30% respectively. At LI diagnosis, liver characteristics were: AST 36 (28–50) IU/L, ALT 35 (25–48) IU/L, MELD 8 (7–10), Child-Pugh 5 (5–5), FIB-4 2.3 (1.4–4.7), liver stiffness (FibroScan®) 8 (6–15) kPa and hepatic venous pressure gradient 6 (4–11) mmHg. Liver biopsy (n = 52) identified vascular porto-sinusoidal disease, advanced fibrosis/cirrhosis, and NASH in respectively 35%, 19%, and 13% of the patients. After a median follow-up of 21 (12–54) months after LI diagnosis, ascites, variceal bleeding, portal vein thrombosis, hepatic encephalopathy and hepatocellular carcinoma occurred in 14%, 13%, 5%, 4% and 2% of the patients respectively. Twelve patients underwent liver transplantation (LT), 5 hematopoietic stem cell graft and 13 lung transplantation. Five-year overall survival rate and LT-free survival rate of patients with LI were 79% and 70% respectively. In multivariate analysis, a FIB-4 score ≥ 3.25 and cofactor of liver disease (alcohol consumption >100 g/week, HBsAg +, metabolic syndrome, BMI >25 kg/m², ferritin >1000 μg/L) independently predicted LT or death (Figure 1).



Conclusion: Liver involvement is frequent but paucisymptomatic. Histological lesions are heterogeneous, including vascular porto-sinusoidal disease and advanced fibrosis/cirrhosis. A FIB-4 score ≥ 3.25 and/or association with excessive alcohol consumption, overweight and iron overload are risk factors for LT or death.

GS04

Gut microbiota drives hepatocarcinogenesis by promoting TLR4-dependent expansion of monocytic myeloid-derived suppressor cells

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Background: Today, the link between intestinal dysbiosis and chronic liver disease is well established. However, molecular mechanisms by which intestinal microbiota affect HCC development and direct antitumor immune surveillance need to be defined. Here, we investigated how NLRP6-mediated intestinal dysbiosis and dynamic microbiota modulation control hepatocarcinogenesis.
Methods: Hepatocyte-specific NEMO/IKKγ knockout mice ($NEMO^{\Delta hepa}$) were used as a model of experimental steatohepatitis. To investigate the impact of NLRP6-mediated intestinal dysbiosis on the inflammatory microenvironment, $NEMO^{\Delta hepa}$ mice were crossed with constitutive *Tlr4* and *Nlrp6* knockout mice. Microbiota of $NEMO^{\Delta hepa}$, $NEMO^{\Delta hepa}$/$Tlr4^{-/-}$ and $NEMO^{\Delta hepa}$/$Nlrp6^{-/-}$ mice were modulated by broad-spectrum antibiotics (ABx) or fecal microbiota transfer (FMT), respectively. Suppressive capacity of myeloid derived suppressor cells (MDSCs) on T-cells was studied in-vitro. Finally, targeted microbiota reconstitution experiments with *Akkermansia muciniphila* were performed.
Results: Intestinal dysbiosis in $NEMO^{\Delta hepa}$/$Nlrp6^{-/-}$ was associated with more pronounced steatohepatitis encompassing elevated liver transaminase levels, leukocyte infiltration and apoptotic cell death, ultimately leading to aberrant hepatocyte proliferation and increased tumor burden in 52 weeks old mice. Interestingly, intestinal barrier function measured by in-vivo FITC permeability was highly correlated with tumor burden and followed by a significantly increased infiltration of $Ly6C^{hi}$ monocytic myeloid derived suppressor cells (mMDSC) and suppression of CD4+ and CD8+ T cells in $NEMO^{\Delta hepa}$/$Nlrp6^{-/-}$. This immune phenotype was transmissible via FMT of dysbiotic $Nlrp6^{-/-}$ microbiota, reversible upon microbiota depletion with ABx and dependent on functional TLR4 signaling. Strikingly, the dysbiotic $Nlrp6^{-/-}$ gut microbiota community of 13 and 52 weeks old mice was characterized by a loss of *Akkermansia muc.*, which correlated with steatohepatitis activity. Targeted reconstitution with *Akkermansia muc.* ameliorated steatohepatitis and dampened mMDSC infiltration.
Conclusion: NLRP6-mediated intestinal dysbiosis drives steatohepatitis progression towards HCC by shaping the hepatic inflammatory microenvironment. Short-term microbiota modulation or targeted microbiota reconstitution closely reshapes the hepatic tumor microenvironment ultimately opening new therapeutic windows for future cancer prevention and therapy.

GS05

Validation of the Model for End-stage Liver Disease sodium score for the Eurotransplant region

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Background and Aims: The shortage of liver grafts results in the prioritization of the sickest patients on the waiting list for liver transplantation. Since 2006, the degree of disease severity in transplant candidates is estimated with the Model for End-stage Liver Disease (MELD) score. However, MELD does not account for the worse prognosis associated with hyponatremia. Since the prevalence of cirrhosis is on the rise, better prediction of mortality and improved allocation for liver transplantation are becoming increasingly important. This study researches the potential impact of using MELD-Na instead of MELD for the allocation of livers in the Eurotransplant region.
Method: All candidates allocated through MELD with chronic liver disease on the Eurotransplant (ET) liver transplant waiting list between 2007–2018 were included. They were followed from first listing to delisting or until 90 days. The relation between MELD and Na values at listing and 90-day mortality was assessed through a multivariate Cox proportional hazard regression. A reclassification table was constructed of the relevant changes in MELD to MELD-Na score. This allowed an estimation of the lives saved if MELD-Na-based allocation would have been used.
Results: 5223 patients were included. After 90 days, 21.3% were transplanted, 24.2% were removed and 2.8% had died. Hyponatremia of <135, <130 and <125 mmol/L was found in respectively 28.5%, 8.8% and 2.6% of the listed patients. Between 140 to 125 mmol/L, the MELD-corrected risk of 90-day death increased by threefold (2.9; 95% CI 2.30–3.53; $p < 0.001$). The hazard ratio for death was 1.16 (95%CI 1.15–1.17; $p < 0.001$) per gained MELD point and 1.08 (95%CI 1.06–1.09; $p < 0.001$) per 1-unit Na decrease. The MELD-Na had a c-index of 0.847 (SE 0.007, $p < 0.001$). Of the deceased patients, 26.3% would have had a significantly higher chance of transplantation with MELD-Na, which equals to a 4.9% decrease in 90-day waiting list mortality.
Conclusion: The ET waiting list population has a relatively high prevalence of hyponatremia. For transplant candidates, a low Na increases the risk of 90-day mortality by threefold. If MELD-Na would have been used, 26.3% of the deceased patients would have had a significantly higher chance of transplantation. The 90-day waiting list mortality would have been lowered by 4.9%. Thus, MELD-Na-based allocation could reduce waiting list mortality for the ET region.

GS06

A randomized, multi-center, double-blinded, placebo controlled, investigator-initiated trial to assess the impact of L-carnitine administration on the quality of life in the liver cirrhosis with covert hepatic encephalopathy

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Background and Aims: Covert hepatic encephalopathy (CHE) leads to poor quality of life (QOL) in liver cirrhosis (LC) patients. We aimed to evaluate the impact of L-carnitine on the QOL evaluated by the 36-Item Short Form Survey (SF-36) in CHE patients following 24 weeks of treatment. Secondary endpoints were the effects of L-carnitine on the improvement of cognitive dysfunction.
Method: We performed a prospective, randomized, double-blinded, placebo-controlled study administering L-carnitine for 24 weeks to LC patients with CHE. Thirteen centers from Korea were engaged. CHE was defined as either West-Haven grade 1 or grade 0 with the Psychometric hepatic encephalopathy score (PHES) below –4. Patients who had previously experienced overt HE were excluded.
Results: A total of 230 LC patients were screened. 150 CHE patients underwent randomization. The mean age was 53 years and 65% were male. Mostly they were chronic hepatitis B and 82% were Child-Pugh A. Seventy two and 70 patients were randomly assigned to the placebo group and the L-carnitine group. Baseline characteristics including results of PHES scores were similar between the groups. Although SF-36 levels were not different between the groups, the differences of SF-36 between the baseline and at 24 weeks of treatment were 2.42 ± 12.86 in the placebo vs. 4.60 ± 11.73 in the L-carnitine groups ($P = 0.001$). Trend analysis for PHES showed significant improvement in the L-carnitine group ($P = 0.023$). The rate correct score of inhibition test among the Korean Stroop Test at 24 weeks of treatment was significantly higher in the L-carnitine group ($P = 0.038$). Additionally, the gap of total carnitine level between the baseline and week 24 were positively correlated with the improvement of rate correct scores of all four components in the Korean Stroop Test ($r = 0.3$ for Color Test; $r = 0.4$ for Word Test; $r = 0.5$ for Inhibition Test; $r = 0.3$ for Inhibition/Switching Test; all P values <0.05) in the L-carnitine group.
Conclusion: Administration of L-carnitine for 24 weeks in the LC patients with CHE were related to improvement of QOL as well as cognitive function.

GS07

Nidufexor, a non-bile acid FXR agonist, decreases ALT and hepatic fat fraction in patients with NASH after 12 weeks dosing

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Background and Aims: Non-bile acid farnesoid X receptor (FXR) agonists have significant therapeutic potential for treatment of non-alcoholic steatohepatitis (NASH). FXR has pleiotropic metabolic effects and agonists with different chemical and pharmacological properties may exert diverse effects. Nidufexor (LMB763) is a FXR partial agonist being evaluated in NASH and renal disorders.
Method: We performed a randomized, double blind, placebo-controlled, study to assess safety, tolerability and biomarker efficacy of nidufexor at 50 mg and 100 mg over 12 weeks of treatment. The study population included those diagnosed with NASH (historical liver biopsy, elevated ALT) or phenotypic NASH (elevated ALT, BMI and Type 2 DM). Primary endpoints were safety and reduction in ALT. Secondary endpoints included hepatic fat (MRI PDFF), pharmacokinetics, lipid profiles and anthropometry.
Results: 121 patients were randomized to placebo (N = 40) or nidufexor at 50 mg (N = 44) or 100 mg (N = 37) and 94 patients (77.7%) completed the study. Following oral administration of nidufexor the mean Tmax was 2 hours; systemic exposure was approximately dose proportional (Cmax on Day 42; 1.29 μM and 2.23 μM) with little accumulation (AUC accumulation ratio 1.3 and 0.9) at 50 mg and 100 mg nidufexor respectively. At Week 12, ALT decreased by 8% (2.5 U/L), 31% (14.3 U/L; p = 0.038) and 33% (18.8 U/L; p = 0.0031) in patients receiving placebo, 50 mg or 100 mg nidufexor. Placebo adjusted geometric mean hepatic fat reduction was 29% and 32% for 50 mg or 100 mg nidufexor (p < 0.0001 Vs placebo). Body weight decreased by 0.31 kg, 1.94 kg (p = 0.012) and 2.1 kg (p = 0.013) in patients receiving placebo, 50 mg or 100 mg nidufexor. Most patients (86.8%) experienced at least one AE, the most common being pruritus, reported in 15%, 29.5%, and 54.1% of placebo, 50 mg and 100 mg nidufexor respectively. There was no significant change in total cholesterol, LDL-C or triglycerides; HDL-C decreased by 12% and 16% in patients receiving 50 mg or 100 mg nidufexor.
Conclusion: In patients with NASH, both dosages of nidufexor appeared safe and were associated with significant reductions in ALT levels, hepatic fat fraction and body weight. The most frequent AE was pruritus, which was more common at 100 mg nidufexor. There were no meaningful changes in total cholesterol, LDL–C or triglycerides, although HDL–C decreased in both active groups. This study reinforces the likely utility of FXR agonism in NASH pharmacotherapy and further defines the range of potential class effects.

Hepatitis B – Translational

AS001

Preclinical assessment of capsid assembly modulators (CAMs) of varying potency revealed a novel class of picomolar-acting CAMs inducing neither significant HBcAg cytoplasmic retention nor adverse interactions with HBcAg-specific adaptive immunity

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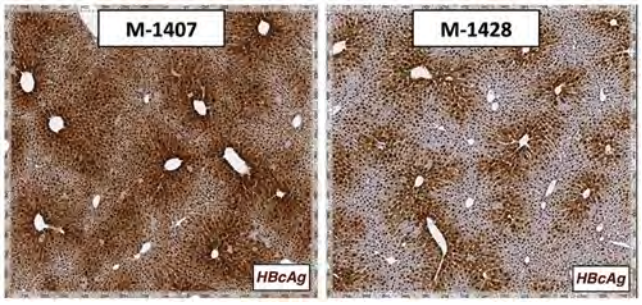
Background and Aims: Capsid assembly modulators (CAMs) that induce the formation of empty/aberrant HBV capsids in the hepatocyte are currently under development. Whether CAMs of different potency in vitro varyingly alter the normal intracellular distribution of the particulate and nonparticulate forms of the HBV core protein (HBcAg) in vivo, and whether such supposed alteration has toxic and/or immunoregulatory/immunopathological consequences is ill defined. The aim of this study was to evaluate these issues, exploiting immunocompetent transgenic mice that - being immune tolerant to HBV - indefinitely replicate the virus at high levels in the liver and display stable and lifelong viremia of ~10^8 HBV genomes/ml.
Method: Three proprietary CAMs (termed M-1103, M-1407 and M-1428) and a first-in-class CAM (termed NVR3-778) endowed with diverse potency profiles in vitro were evaluated in HBV-replicating transgenic mice (transferred or not with HBcAg-specific mouse naïve or effector CD8 T cells) as per i) relative antiviral potency, ii) capsid/core protein distribution, iii) direct or immune-mediated hepatocellular toxicity and iv) immunoregulatory potential.
Results: EC50/EC90 evaluation in HepAD38 cells and HBV-infected HepG2-NTCP cells indicated that M-1103 and M-1407 are ~30 and ~100-fold more potent in vitro than NVR3-778, respectively; potency increased to ~ 500 folds in the case of the picomolar-active M-1428. Similar potency ratios over NVR3-778 were observed in vivo, with M-1428 quantitively eliminating HBV replicative intermediates from the liver of transgenic mice after only 3 days of dosing at 50 mg/kg QD (with commensurate reductions in serum HBV DNA, HBV RNA and HBeAg). Time- and dose-dependent experiments revealed that none of the tested CAMs caused direct liver injury. Surprisingly, however, NVR3-778, M-1103 and M-1407 induced significant cytoplasmic retention of HBcAg, whereas the more potent M-1428 and structurally related analogues with increased potency did not. Of note, the latter compounds did not sensitize hepatocytes to HBcAg-specific effector CD8 T cell-mediated killing and did not interfere with a recently described IL-2-based therapeutic strategy (*Nature* 574:200, 2019) capable of reverting T cell tolerance in this same animal model.



Conclusion: This study revealed that CAMs endowed with highly diverse antiviral potency in vitro behave in vivo quite unpredictably as per their intrinsic capacity to retain cytoplasmic HBcAg and, secondarily, influence the interaction of CAM-exposed HBV-expressing hepatocytes with adaptive immune responses.

AS002

Targeting inhibitor of apoptosis proteins (IAPs) enhances intrahepatic antiviral immunity to clear hepatitis B virus infection in vivo

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Background and Aims: The chronic infection caused by hepatitis B virus (HBV) remains hard to cure by current antiviral therapies. Previous studies had shown that the inhibitor of apoptosis proteins (IAPs) prevented TNFα-mediated killing of infected hepatocytes and

resulted in HBV persistence. APG-1387 is a novel bivalent antagonist of IAPs targeting IAPs and is well tolerated in clinical trials of cancer therapy. Here, we evaluated the anti-HBV function of APG-1387 and explored the underlying mechanisms in *vivo*.
Method: Three immunocompetent HBV carrier mouse models were established by infection with recombinant rAAV8-HBV1.3 in C57BL/6j mice or hydrodynamically injected with pAAV-HBV1.2 plasmid to C57BL/6j and C3H/HeN mice strains. 20 mg/kg of APG-1387 was injected by i.v. or i.p. once weekly. Quantification of viral DNA, antigens and transaminases in serum and liver samples were examined. Cell apoptosis were determined by TUNEL or cleaved-caspase-3 immunofluorescence staining. Intrahepatic T cell responses were analyzed by flow cytometry. Transcriptomic analysis of liver tissues after therapy was performed by RNA-seq.
Results: Compared to vehicle injection, APG-1387 treatment for 4–20 weeks in different models led to completely clearance of HBsAg, HBeAg and HBV DNA in serum, as well as HBcAg and HBV replicative intermediates in infected livers, and no relapse after stop therapy. After APG-1387 injection, cleaved-caspase-3 expression in HBcAg-positive hepatocytes was detected, and serum transaminase levels were transiently elevated and its peak levels were associated with the baseline HBsAg levels. However, pan-caspase inhibitor Emricasan or Z-VAD-FMK treatment could not block the antiviral effect of APG-1387. Furthermore, clearance of HBV by APG-1387 was found to be associated with upregulation of intrahepatic HBV-specific CD4+ and CD8+ T cells frequency and function. As expected, APG-1387 was unable to clear HBV in TNFα, CD4 or CD8 deficiency mice. Finally, Gene Set Enrichment Analysis of RNA-seq data showed that multiple immune-related genes were upregulated by APG-1387, similar to the genes induced in the liver during HBV clearance in chimpanzees.
Conclusion: These findings indicated that APG-1387 was able to clear chronic HBV infection in various mouse models with a unique induction of apoptosis and immunoregulation mechanism. Application of IAP antagonist might represent a novel immunotherapeutic strategy for HBV functional cure.

AS003
Serum and intrahepatic HBV markers and HBV-specific CD8 T cell responses after nucleos(t)ide analog therapy discontinuation in HBeAg-negative chronic hepatitis B patients
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Background and Aims: Previous studies have reported that up to 20% of patients with chronic hepatitis B (CHB) may achieve functional cure (HBsAg loss) after nucleos(t)ide analog (NA) treatment withdrawal. CD8 T cells play an important role in the immune control of HBV infection. The objective of this study was to analyze HBV-specific CD8 responses in parallel with peripheral and intrahepatic virological markers after NUC discontinuation in patients with HBeAg-negative (HBeAg-) CHB.
Method: Twenty-seven HBeAg- CHB patients with complete viral suppression (>3 years) and without cirrhosis were prospectively studied. A liver biopsy was taken at the time of treatment withdrawal (baseline). PBMC and serum samples were collected at baseline and various time-points during follow-up. Intrahepatic HBV-DNA (iHBV-DNA), covalently closed circular DNA (cccDNA) and serum HBV-DNA, HBsAg, core-related antigen (HBcrAg) and pregenomic RNA (pgRNA) levels were determined. HBV-specific T cell responses (IFNγ, TNF and CD107a) were analyzed by multiparametric flow cytometry after in vitro expansion in the presence of overlapping peptides (OLP) spanning core, envelope and polymerase.
Results: After a median follow-up of 34 months (IQR 26–37), 22 (81%) patients remain off-therapy, with 8 (30% of the total cohort) losing HBsAg; whilst 5 (19%) required NA reintroduction due to relapse. Although all patients were iHBV-DNA and cccDNA positive at baseline, only 41% and 48% had detectable serum pgRNA and HBcrAg, respectively. Baseline HBsAg levels correlated significantly with iHBV-DNA ($r = 0.7$, $p < 0.0001$) and both markers were lower in patients who lost HBsAg ($p < 0.001$). Baseline intrahepatic (iHBV-DNA, cccDNA) or serum (HBsAg, HBcrAg or pgRNA) viral markers did not show any association with peripheral CD8 T cell responses. Importantly, degranulating CD8 T cells (CD107a+) or those co-producing IFNγ and TNF in response to stimulation with core OLP were significantly higher ($p = 0.05$ and $p = 0.039$, respectively) at baseline in patients remaining off-therapy compared to those requiring NA reintroduction. Interestingly, the enhanced frequency of CD8 T cells co-producing IFNγ and TNF persisted up to 1 year of follow-up ($p = 0.009$). Notably, CD8 T cell responses to polymerase or envelope failed to associate with outcome as robustly as those against core.
Conclusion: NA discontinuation is feasible in a high proportion of HBeAg- patients, particularly in those with low HBsAg levels. Higher frequencies of CD8 T cells with cytotoxic and non-cytolytic anti-HBV (core) reactivity are detectable at baseline in those patients who maintain viral control after therapy withdrawal. These data support HBsAg levels and HBV-specific CD8 T cell frequencies as correlates of HBV control off-therapy, requiring validation in larger studies.

AS004
Targeted long read sequencing reveals the comprehensive architecture and expression patterns of integrated HBV DNA in CHB liver biopsies
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Background and Aims: Hepatitis B virus (HBV) integration into the host genome has been implicated in the development of hepatocellular carcinoma and has been observed with PCR-based assays or short read sequencing, but limitations of these methods have prevented the full characterization of integration events. Here, we use an HBV-targeted sequencing strategy to determine the full architecture of HBV integrations in the liver of chronically-infected HBV (CHB) patients. We define the full sequences of integrated HBV DNA and compare these sequences with data from RNA-Seq to determine productive vs non-productive integrations.
Method: 28 liver biopsies were obtained from CHB patients enrolled in Gilead Clinical Trial GS-US-174-0149 with an even distribution of HBeAg positive and negative samples, including five samples taken 96 weeks post-baseline. Genomic DNA was sheared to 7 kb fragments, barcoded for multiplexing, and enriched for HBV using the IDT xGen platform with a custom panel of biotinylated 120 bp probes targeted to HBV genotypes A through H. Enriched DNA libraries were sequenced using a Pacific Biosciences Sequel II (PacBio) and compared to corresponding RNA-Seq.
Results: Target enrichment increased detection of HBV sequences, and the PacBio platform produced high quality reads that were several kilobases long, many of which contained the entire viral integration sequence and thousands of base pairs of adjacent host sequences within a single read. In contrast, short read whole genome

sequencing data only detected virus-host junctions. We also observed transcripts resulting from non-integrated HBV as identified by the presence of 3.2 kb reads exclusive of host sequences. Host/HBV chimeric reads were compared to RNA-Seq data from the same biopsies to match transcripts with specific integration events. Several partial integration events, not associated with HBV direct repeats (DR1 and DR2), were identified and appeared transcriptionally silent despite being inserted in or near host gene loci. Most transcribed integrations contained HBV promoter sequences driving S transcript expression and are associated with the HBV DR1 region.
Conclusion: Targeted long-read sequencing provides better accuracy and deeper coverage, compared to whole genome sequencing. This assay can elucidate full primary sequence of integrated HBV, and, when paired with RNA-Seq data, can show the differences between transcriptionally active and inactive events.

AS005

Transcriptome analysis of paired liver biopsies identifies correlates of HBsAg response in placebo and TDF treated CHB patients

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Background and Aims: Intrahepatic evaluation of host immunity can provide insight into events leading to important clinical events in patients with chronic hepatitis B (CHB) infection. Here we investigate baseline and year 3 liver biopsies from a randomized placebo-controlled trial of Tenofovir Disoproxil Fumarate (TDF) in CHB patients (IN-US-174-0178) with minimally elevated aminotransferase for gene expression signatures associated with clinical response.
Method: CHB patients (N = 130) with serum ALT 1-2x upper limit of normal (ULN) with no clinical liver cirrhosis or decompensation were randomized into TDF and Placebo 3-year treatment arms. Liver biopsies were taken at baseline and year 3. Gene expression from liver biopsies was quantified with salmon software and gene set enrichment was interrogated using GSEA software package (Broad Institute) and pathway gene signatures from MSigDB database.
Results: Overall, at year 3 patients treated with TDF displayed significantly reduced inflammatory response (False Discovery Rate, FDR = 0.001), while gene signatures for fatty and bile acid metabolism and adipogenesis were significantly upregulated (FDR < 0.001), suggesting improved liver function. Nine and 16 patients in the placebo and TDF arms, respectively, experienced HBsAg reduction greater than 0.5 Log10 IU at year 3. Compared to HBsAg non-responders, these HBsAg responders at baseline demonstrated upregulation of B cell activation (FDR = 0.006) as well as IFN alpha (FDR = 0.008) and IFN gamma response (FDR = 0.081). In addition, placebo responders exhibited elevation of innate immune response (FDR = 0.022) and TNF alpha signaling (FDR < 0.001) compared to placebo non-responders, whereas TDF responders demonstrated enrichment B cell activation signatures (FDR = 0.021) and B cell proliferation (FDR = 0.061) compared to TDF non-responders. Comparison between placebo and TDF HBsAg responders revealed that placebo responders (NPlacebo = 9; NTDF = 16) again exhibited stronger upregulated IFN-alpha (FDR < 0.001) and IFN-gamma (FDR < 0.001) signaling pathways at baseline (Figure 1), suggesting different pathways for HBsAg reduction by natural history and antiviral treatment.
Conclusion: Our results demonstrate that HBV control is linked to interferon and humoral immune response and suggest that immunotherapies aimed to boost these immune responses may act synergistically with nucleotide analogue therapy to achieve sustained control of HBV.

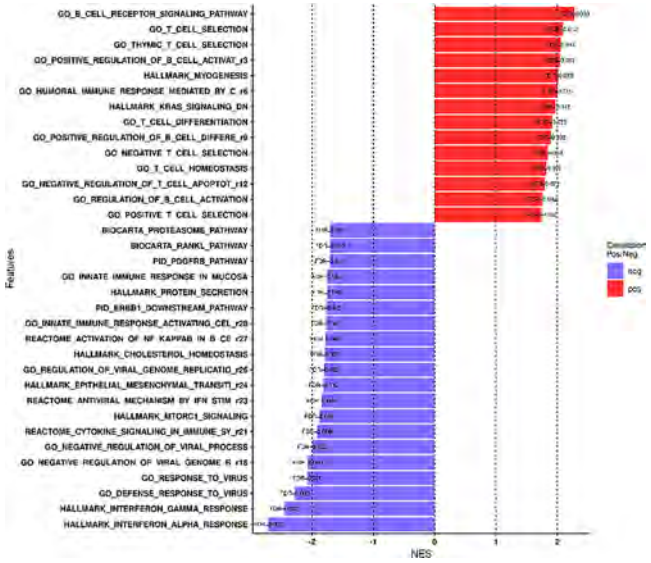

Figure: Gene Signature Enrichment Analysis comparing TDF and Placebo HBsAg responders (>0.5 Log10 HBsAg reduction at year 3) at baseline. Negative NES (Normalized Enrichment Score) represents feature upregulation in the Placebo arm, whereas positive NES identifies upregulated features in the TDF arm.

AS006

Prospective study of HBV cccDNA kinetics in a French multicenter cohort of liver transplant patients (ECOGREFFE) reveals very early graft infection despite NUC+HBIG prophylaxis

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Background and Aims: Combined Nucleoside Analogues (NAs) and hepatitis B immunoglobulins (HBIG) therapy accounts for the low risk of HBV recurrence after liver transplantation (LT). The duration of the double prophylaxis remains a matter of debate and the lack of non-invasive biomarkers for intrahepatic HBV replication prevents the implementation of personalized duration of treatment.
Method: Blood samples from 34 patients transplanted for HBV-related disease were collected at LT registration, the day of the LT, 3 and 12 months after LT. A tissue sample from the native liver, after liver reperfusion and at 12 months after LT were collected and snap frozen at −80°C. Intrahepatic HBV cccDNA, DNA replicative intermediates (tHBV DNA) and 3.5Kb-RNA were quantified by digital-droplet PCR. Serum HBcrAg and quantitative HBsAg were analysed using the Lumipulse platform (Fujirebio - LLOQ of 3 logU/ml and 5 mIU/ml, respectively).
Results: At the time of LT, serum HBV DNA was undetectable in 86.2% of patients. The median age was 54.3 years, 24 had hepatocellular

carcinoma, 28 were HBeAg-negative and 2 were co-infected with HDV. HBV DNA was detectable in 97% of the native livers with a median value of 0.036 copies/cell for tHBV DNA and 0.0012 copies/cell for cccDNA. 3.5 Kb RNA was found in 20 patients with a median of 0.0029 copies/cell. All recipients received NA and 1-year HBIG treatment after LT and had undetectable serum HBV DNA 1 year post-LT. 14/29 reperfusion biopsies were positive for HBV DNA and 3 were positive for 3.5 Kb RNA. 13/20 liver biopsies available 1 year post-LT were positive for HBV DNA and 7 for 3.5 Kb-RNA with a mean of 0.006 copies/cell for tHBV DNA, 0.0006 copies/cell for cccDNA and 0.0012 copies/cell for 3.5Kb RNA. Pre-LT serum HBcrAg was significantly correlated with native liver tHBV DNA ($r = 0.67$, $p < 0.0001$), cccDNA ($r = 0.56$; $p = 0.0004$) and 3.5 Kb-RNA ($r = 0.71$; $p < 0.0001$). Pre-LT qHBsAg correlated with native liver tHBV DNA ($r = 0.63$; $p = 0.0003$) and 3.5 Kb-RNA ($r = 0.62$; $p = 0.0005$) but not with cccDNA levels. At 3 months and 1 year post-LT, 7 and 5 patients, respectively, were still positive for serum HBcrAg. Albeit negative with classic techniques, 5 patients scored positive for HBsAg 1 year post-LT by highly sensitive Lumipulse test.

Conclusion: Our study shows a rapid HBV infection of the graft despite NA + HBIG prophylaxis. One year post-LT, a majority of patients had detectable intrahepatic HBV markers. No direct correlation between pre-LT serum HBcrAg and HBsAg with HBV recurrence was identified. Correlation of intrahepatic HBV markers with serum circulating HBV RNAs is under investigation.

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Liver transplantation

AS007

International, multicenter study on the outcome of locoregional therapy before liver transplant for hepatocellular carcinoma extending the Milan criteria

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Background and Aims: After downstaging of patients with hepatocellular carcinoma (HCC) beyond the conventional criteria, a similar outcome for liver transplant has been shown compared to patients initially meeting the Milan criteria. We aimed to evaluate the effect of locoregional therapy during waiting time on the outcome after liver transplant by comparing patients within the Milan criteria with the group meeting the University of California San Francisco downstaging protocol (UCSF-DS) and the "All-comers" beyond these inclusion criteria. We also assessed the role of alpha-fetoprotein (AFP) in predicting HCC recurrence in the downstaging groups.

Method: This international, multicenter cohort study included 2,444 consecutive adult patients with liver transplantation for non-metastatic HCC in 47 centers from France, Italy, Belgium and Latin America (2000–2018). Pre-transplant tumor characteristics and serum AFP levels were obtained at diagnosis, listing, last imaging evaluation prior to liver transplant and explant pathology analysis. Survival and cumulative recurrence were compared at listing and last evaluation prior transplantation according to the Milan criteria and UCSF-DS protocol. Multivariate Cox regression models, with hazard ratios (HR) and 95% confidence intervals (CI) were conducted. Further competing risk regression analysis was carried out for HCC recurrence (competing event was considered any death without prior recurrence).

Results: At listing, 1978 patients were within Milan criteria (80.9%), 295 met the UCSF-DS protocol (12.1%) and 168 (6.9%) were All-comers. Median time on waiting list was 5.5 months. Similar post-transplant survival and higher recurrence cumulative incidence rates were observed for the UCSF-DS group [SHR 1.64 (CI 1.15–2.35); $p = 0.007$] and All-comers [SHR 3.69 (CI 2.65–5.14); $p < .0001$] compared to Milan criteria at listing. After locoregional bridging therapies, effective downstaging to Milan criteria at last evaluation prior to transplant was achieved in 47% (CI 37–57%) of the UCSF-DS group and in 38% (CI 26–52%) of All-comers. After effective downstaging, similar recurrence and survival rates were observed between the Milan and UCSF-DS group, whereas a higher recurrence [SHR 6.1 (CI 3.10–11.9); $p < 0.0001$] was observed in the All-comers. An AFP value at listing more than 20 ng/ml was associated with a higher risk for recurrence [SHR 1.75 (CI 1.05–2.9); $p = 0.015$] and lower survival [HR 2.20 (CI 1.34–3.59); $p = 0.002$] among patients in the UCSF-DS group.

Conclusion: Although the efficacy of downstaging to Milan criteria was lower than fifty percent, survival and recurrence rates were similar in patients within UCSF-DS criteria successfully downstaged when compared to patients initially within the Milan criteria at listing. An AFP value below 20 ng/ml might be an additional clinical tool to select better candidates in the UCSF-DS group.

AS008

Share MELD-35 does not fully address the high waiting list mortality of patients with acute on chronic liver failure grade 3

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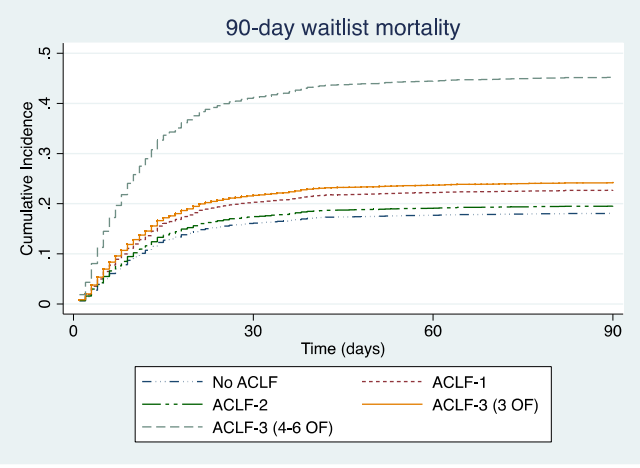
Background and Aims: Patients with acute on chronic liver failure grade 3 (ACLF-3) have the highest risk for waitlist mortality. The share

MELD-35 rule was introduced in the USA in 2013 to allow regional sharing of organs, to reduce the high mortality rates of patients with MELD ≥ 35. Although this change has reduced mortality for patients with high MELD-Na scores, by enabling regional sharing, its impact on patients with ACLF-3 is unknown. Our aims were to determine whether share MELD-35 addresses the high mortality on the waiting list of patients with acute on chronic liver failure grade 3 (ACLF-3).
Method: We studied the UNOS database, years 2010–2017. ACLF was identified using the EASL-CLIF definition. We assessed the effect of the share 35 rule according to year of LT, specifically years 2010–2012 considered pre-share 35 and years 2014–2016 designated post-share 35. We evaluated outcomes of 90-day waitlist mortality using competing risks regression analysis.
Results: We identified 6,342 candidates at listing with a MELD-Na score > = 35, of which 3,122 patients had ACLF-3. Among those with ACLF-3, extra-hepatic organ failures were significantly more prevalent in patients with 4–6 organ failures. Competing risks regression, adjusting for age, etiology of liver disease, and MELD-Na score, revealed that candidates listed with ACLF-3 had a significant risk for 90-day waitlist mortality (SHR = 1.76; 95% CI 1.27–2.44), particularly those with four or more organ failures (SHR = 3.01; 95% CI 2.15–4.24). (Figure) ACLF-1 and ACLF-2 were not associated with greater mortality relative to no ACLF. Organ failures with the strongest association for waitlist mortality included mechanical ventilation (SHR = 1.89; 95% CI 1.67–2.15), circulatory failure (SHR = 1.64; 95% CI 1.45–1.86) and brain failure (SHR = 1.16; 95% CI 1.03–1.33). LT occurring post-share 35 was associated with reduced 90-day waitlist mortality among patients listed with ACLF-3 and MELD-Na score ≥ 35 (SHR = 0.58; 95% CI 0.49–0.69). However, among patients with 4–6 organ failures, LT after share 35 implementation was not significantly associated with reduced waitlist mortality (SHR = 0.79; 95% CI 0.60–1.05).



Conclusion: Although regional sharing of organs for patients with MELD ≥ 35 is associated with a significant reduction in waitlist mortality, patients with ACLF-3, particularly those with extra-hepatic organ failures are not fully addressed by this scheme. Incorporation of ACLF grading into organ allocation schemes may allow more equitable distribution of organs.

AS009

Pretransplant rifaximin administration reduces posttransplant liver injury and early allograft dysfunction in mouse and human liver transplantation

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Background and Aims: Rifaximin commonly used to treat hepatic encephalopathy is a minimally absorbed antibiotic. Gut-liver axis is considered to play an important role in hepatic injury, and its microbiota is receiving increased attention in the field of organ transplantation. We examined the effectiveness of rifaximin treatment in mice and human liver transplant (LT) recipients on hepatocellular graft injury.
Methods: In the experimental arm, livers from C57BL/6 mice were transplanted to allogeneic BALB/c mice after 18 h of cold-storage. To examine the impact of gut microbiota, fecal microbiota transplant (FMT) was performed prior to LT in three major groups (n = 4/grp): Gr. I - control (naïve untreated); Gr. II - rifaximin (7d rifaximin treatment prior to LT); Gr. III - rifaximin + FMT (7d rifaximin treatment + FMT from naïve mice). In the clinical arm, 447 adult primary LT recipients were retrospectively reviewed and classified based on the duration of pre-LT rifaximin therapy: Gr. I - rifaximin (≥ 7d); and Gr. II - control (<7d).
Results: In mouse LT recipients, rifaximin treatment prevented hepatocellular damage, evidenced by lower serum transaminase levels as compared to control or rifaximin + FMT groups (control vs rifaximin vs rifaximin + FMT vs control, mean ALT (IU/L): 8132 vs 3197 vs 8897, resp., $p < 0.05$). In addition, LT in rifaximin group showed significantly lower Suzuki's histological score of hepatocellular injury; and lower CD68 (macrophage)/Ly6G (neutrophil) infiltration as compared to control or rifaximin + FMT group ($p < 0.05$). In the clinical arm, 260 LT patients who underwent ≥7d rifaximin treatment were characterized by significantly lower maximum postoperative serum ALT levels within 7 POD (409 vs 571 IU/L, $p < 0.001$) and depressed occurrence of early allograft dysfunction (EAD; 22.7 vs 31.0%, $p = 0.048$) as compared with controls. Notably, multivariate analysis identified pre-LT rifaximin treatment of <7d as an independent risk factors for development of EAD (Odds ratio: 1.917, $p = 0.008$), along extended cold ischemia time ($p = 0.003$), higher donor age ($p = 0.003$), and larger amount of blood transfusions ($p = 0.019$).
Conclusion: We demonstrated the effectiveness of rifaximin therapy prior to LT in mice and humans, assessed by graft hepatocellular damage and EAD. As rifaximin-mediated benefits were negated by concomitant FMT from normal mice, targeting gut microbiota has a therapeutic potential to prevent post-LT injury and improve clinical outcomes.

AS010

Reassessment of the risk of recurrence (R3) after liver transplantation for HCC: validation of the R3 v.2 score and comparison with existing models: results of a multinational analysis in 2,444 patients

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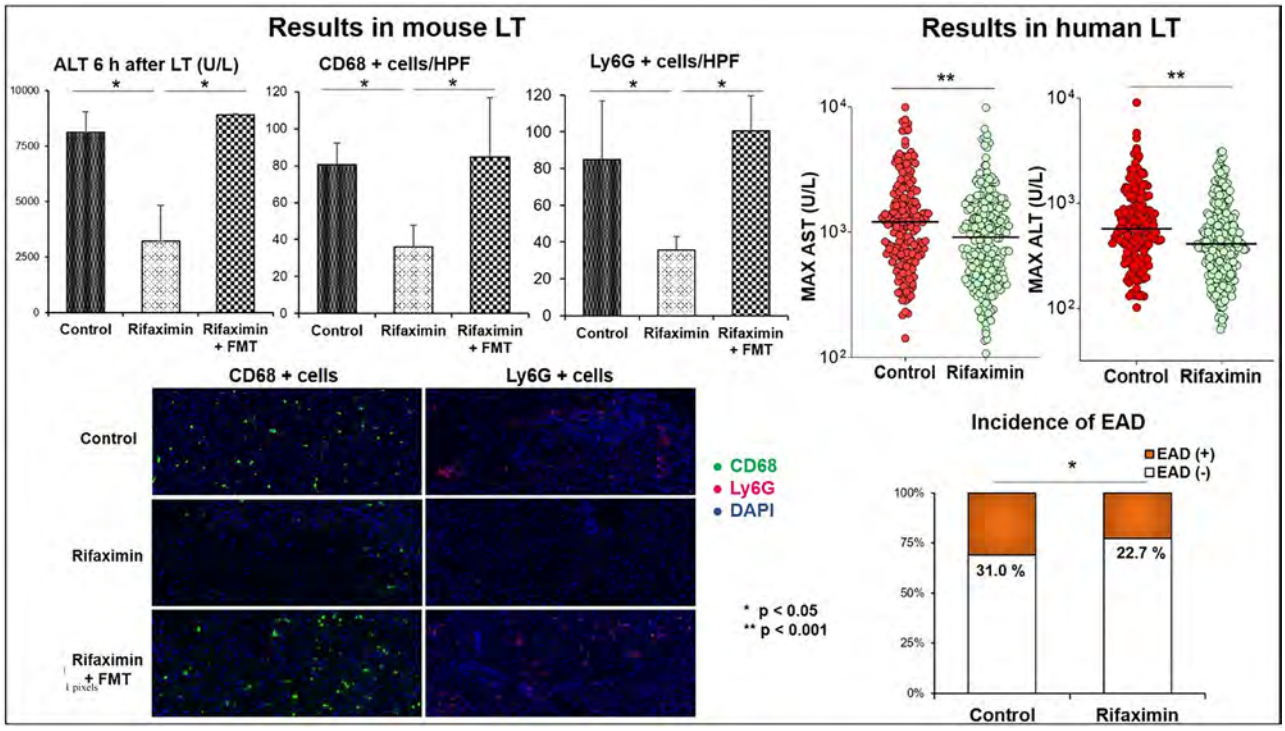

Figure: (abstract: AS009)

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Background and Aims: Patients with hepatocellular carcinoma (HCC) are selected for liver transplantation (LT) based on pre-LT imaging ± AFP level but discrepancies between pre-LT imaging and explanted liver findings are frequent. Our aim was to design an explant-based Recurrence Risk Reassessment (R3) model in patients transplanted for HCC to reassess the risk of recurrence after LT.
Method: A multicenter multinational cohort study of consecutive adult patients with HCC and a first LT in 47 centers from France, Italy, Belgium and Latin America was included (2000–2018). In a TEST cohort from Europe (n = 1359), an explant-based model was design and further evaluated in an external VALIDATION cohort from Latin America (n = 1085). Explant liver findings included macroscopic and microscopic evaluation of each nodule, number and diameter (cm) of each, presence of microvascular invasion (mvi) and degree of tumor differentiation. Multivariate Cox regression models, with hazard ratios (HR) and 95% confidence intervals (CI) were conducted. Further competing risk regression analysis was performed for HCC recurrence (competing event was considered any death without prior recurrence) with sub-HR calculated. We estimated Harrell's C and Somers' D predictive power for HCC recurrence for comparison of different explant based predictive models including: Milan criteria, the Up-to 7, RETREAT score.

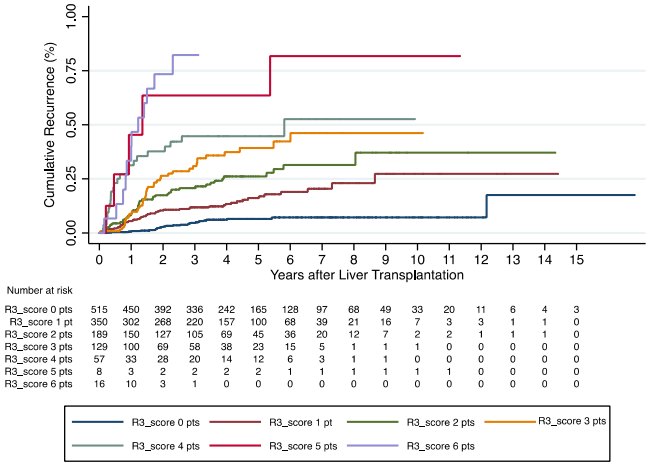

Figure: R3 score as continuous variable SHR 1.97 (CI 1.80–2.16).

Results: In the TEST cohort, variables at explant pathology independently associated with recurrence were number of nodules [1–3 nodules vs ≥4 nodules SHR 1.77 (CI 1.30–2.40)], major nodule diameter [3 cm vs 3–6 cm SHR 2.0 (CI 1.50–2.77) vs >6 cm SHR 6.0

(CI 3.87–9.3)] and presence of microvascular invasion [SHR 2.81 (CI 2.09–3.79)]. Based on this multivariable model, a R3 score ranging from 0 to 5 points was developed. The R3 score was associated with recurrence with a 2 fold increasing cumulative incidence of recurrence for every increasing point (Figure). A cut-off of 1 point was selected as highly associated with HCC recurrence [SHR 0.20 (CI 0.15–0.27); P < 0.0001]. Harrells' c-statistic was higher for the R3 score either as continuous or dichotomous cut-off [0.75 (CI 0.71–0.78)] when compared to Milan, RETREAT and the Up-to 7 models in the TEST cohort. In the external VALIDATION cohort, again the R3 score could stratify two recurrence risk populations with a SHR of 0.22 (CI 0.15–0.32).

Conclusion: A new simple R3 model improves prediction of recurrence compared with other explant-based and composed models for HCC recurrence. The R3 score may be useful to adjust HCC surveillance strategies after LT and may provide a framework for risk stratification in the design of adjuvant therapy clinical trials.

AS011

Long-term results of the first study of early liver transplantation for alcoholic hepatitis

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Background and Aims: Severe alcoholic hepatitis (AH) refractory to medical therapy is associated with a 6-month mortality of more than 70%. We reported in 2011 that early liver transplantation (eLT), in extremely carefully selected patients with corticosteroid-resistant AH, could been performed with promising short-term results. After this initial experience, several studies from the United States on similar outcomes in these patients have been published. The aim of the present study is to report the long-term results in the cohort of patients initially reported in 2011, with the addition of more recent transplanted patients in the same centers and according to the same inclusion criteria.

Method: The seven transplant centers who participated to the initial pilot study published in 2011 selected patients with severe AH who were considered to be candidates for eLT, according to the following criteria: nonresponse to medical therapy, severe AH as the first liver-decompensating event, presence of close supportive family members, absence of severe coexisting or psychiatric disorders, and agreement by patients to adhere to lifelong alcohol abstinence. Patients were included between November 2005 and December 2012. End-points of the present retrospective analysis were patients' survival and rate of (severe) alcohol relapse. Alcohol use was assessed at short intervals during informal interviews of patients and their families as previously described. The final follow-up was on May 31, 2019.

Results: Sixty eight patients (69% of male; median age of 51 years; 95% CI 46–54 yrs) with severe AH that had failed to respond to medical therapy underwent eLT in the seven participating centers. Median discriminant function on the first day of therapy was 72 (95% CI 58–87) and median MELD score was of 31 (95% CI 28–35). Sepsis and hepatorenal syndrome rates before eLT were 47 and 54%, respectively. AH was confirmed in all cases by histological analysis of explanted livers. 84% of patients were treated with steroids for a median duration of 7 days (95% CI 7–8); median Lille score after 7 days of medical therapy was of 0.87 (95% CI 0.33–0.99). After a mean length of follow up after eLT of 59.6 months, severe alcohol relapse reached 10.3% (7/68). Among them, two developed recurrent alcoholic cirrhosis and died. After eLT, overall patients' survival was 82.6 ± 5% at 1 year, 70 ± 6% at 5 years and 56 ± 7% at 10 years. Twenty four patients (35%) deceased from sepsis (n = 7), head-neck cancer (n = 6), major cardiovascular event (n = 4), recurrent alcoholic cirrhosis (n = 2), and others causes (n = 5).

Conclusion: Our results on a large cohort with long follow-up confirm that AH could be a good indication for LT in selected patients; survival is impaired by early death related to severity of liver failure and later because of alcohol-related co-morbidities, especially de novo malignancies.

AS012

Non-alcoholic steatohepatitis (NASH)-related cirrhosis is not associated with lower patient eligibility for liver transplantation compared to other liver disease aetiologies

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Background and Aims: NASH is a growing indication for liver transplantation, however there are concerns regarding transplant eligibility of patients because of the high prevalence of metabolic comorbidities. We compared transplant listing rates of NASH-related cirrhosis to other aetiologies in consecutive patients referred for transplant assessment.

Method: We retrospectively evaluated patients with end-stage liver disease at their first contact in the Transplant Assessment Clinic, Royal Free Hospital, London, United Kingdom. From September 2011 to February 2019, 444 patients (66.7% male, mean age 53.7 ± 10.9 years) underwent assessment which consisted of a first clinic appointment followed by a dedicated cardiac, respiratory, psychiatric, anaesthetic and surgical assessment, in selected patients. Final decision on eligibility status for Orthotopic Liver Transplant (OLT) was obtained in multi-disciplinary meetings.

Results: Alcoholic liver disease (ALD) was the most common indication for referral (35.4%), followed by NASH (20.7%), viral hepatitis (17.1%), autoimmune-related disease (14.9%) and other aetiologies (12%). Patients with NASH cirrhosis (n = 92) had a mean age of 60 ± 7 years, 71.7% of them had diabetes, 23.9% of them had hypertension and 5.4% of them had positive history of cardiovascular disease. Overall, 52.1% of patients were listed for OLT. Patients with NASH showed the highest eligibility for OLT (67%), followed by the autoimmune (65.2%) and the viral group (55.3%) (p < 0.001). Patients with ALD presented the lowest eligibility (34.9%). Among patients not adjudicated as candidates for transplantation, liver improvement was the leading reason for exclusion in all groups (ranging from 19.2% to 34.8%). Frailty was also common in most groups, but its prevalence was lower in NAFLD patients (6.7%). As expected, alcohol misuse was high in ALD patients who were deemed ineligible for OLT (Table).

Table: Counts and percentages of patients that were not listed for OLT according to different aetiology

	NAFLD		ALD		VIRAL		AUTOIMMUNE	
	N	(%)	N	(%)	N	(%)	N	(%)
Liver improvement	10	33.3	19	19.2	11	32.4	8	34.8
Frailty	2	6.7	10	10.1	5	14.7	5	21.7
Co-morbidities	2	6.7	6	6.1	3	8.8	5	21.7
Alcohol abuse	–	–	16	16.2	2	5.9	–	–
HCC out of Milan criteria	2	6.7	7	7.1	3	8.8	–	–

Conclusion: In a tertiary high-volume centre, half of end-stage liver patients fulfilled the criteria for OLT. Contrary to common belief, patients with NASH presented the most favourable listing profile (despite older age and higher prevalence of metabolic comorbidities). Spontaneous liver improvement abrogated the need for transplantation in almost one third of evaluated subjects. Importantly, frailty

and alcohol history/misuse were adverse predictors of successful transplantation listing.

NAFLD – Target identification and drug pipeline

AS013

MBOAT7, HSD17B13 and metabolic risk factors in the progression of PNPLA3-associated steatohepatitis

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Background and Aims: Carriers of the adiponutrin (*PNPLA3*) p.I148M variant have an increased risk of (non-)alcoholic fatty liver disease (NAFLD) and fibrosis (Krawczyk et al. *J Lipid Res* 2017). Furthermore, mutations in the *MBOAT7* gene worsen hepatic fibrosis and hepatocellular damage, whereas a splice variant of *HSD17B13* reduces the general risk of chronic liver disease (CLD) and fatty liver progression (Abul-Husn et al. *N Engl J Med* 2018). Here, we aim to investigate how the *MBOAT7* and *HSD17B13* variants affect steatosis and fibrosis in *homozygous* carriers of the *PNPLA3* risk variant p.I148M.
Methods: In total, 2,278 patients with CLD were screened for the *PNPLA3* variant. Clinical, laboratory and imaging data were collected, including non-invasive liver stiffness measurements (LSM) and controlled attenuation parameter (CAP) by transient elastography. *MBOAT7* rs641738 and *HSD17B13* rs72613567 were genotyped by PCR-based allelic discrimination assays, and genotype-to-phenotype correlations were analysed.
Results: Overall, 144 patients (6.3%) were carriers of the homozygous *PNPLA3* p.148MM genotype (59.7% men, age 18–83 years, 19.7% diabetes). Median CAP was 279 dB/m and median LSM was 12.0 kPa, consistent with advanced fibrosis and steatosis in these patients. The fibrosis stages in NAFLD patients were associated with metabolic risk factors (diabetes, BMI, age), but not *MBOAT7* genotypes. The incidence of cirrhosis and hepatocellular carcinoma was not influenced by *MBOAT7* alleles either. However, a decrease of hepatic steatosis, as measured by CAP, per additionally mutated *MBOAT7* allele was found (−23 dB/m, p = 0.019). Of note, the maximum LSM and CAP in patients with the protective *HSD17B13* genotype were on average 41 kPa and 58 dB/m lower than in carriers of the common allele.
Conclusions: Since a decrease of steatosis in patients with end-stage CLD represents an unfavorable prognostic marker, patients with both homozygous mutated *PNPLA3* and *MBOAT7* allele could represent a vulnerable group of NAFLD patients in whom exogenous factors confer significant risk. The *HSD17B13* splice variant mitigates in part the harmful effects conferred by *PNPLA3* homozygosity.

AS014

The combination of elafibranor and semaglutide drastically improves fibrosing steatohepatitis and distinctly modulates liver inflammatory signature

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Background and Aims: High prevalence of diabetes among patients with NASH prompted us to investigate the combination of elafibranor (ELA) with the anti-diabetic drug semaglutide (SEMA). The aim of this study is to explore the complementary actions of ELA and SEMA in NASH reversal.
Method: Male C57BL/6J mice were fed with the AMLN diet for 35 weeks. Mice with biopsy-confirmed significant steatosis and fibrosis were randomized into treatment groups (n = 12–14). Mice received vehicle, ELA (10 mg/kg/day, PO), SEMA (0.3 nmol/kg, SC) or combination of both drugs for 12 weeks. Submaximal drug doses were used in this study.
Results: At inclusion, mice were obese (41 g), had a severe NASH phenotype (NAFLD activity score (NAS) between 5 and 7, and fibrosis stage of at least 2). Following 12 weeks of treatment with the ELA/SEMA combo, NAS decreased by 3 stages in 14% of mice, and by 2 stages in 44% of mice. This drop was accounted for by a decrease in both steatosis and activity index. None of the mice that received either a low dose of ELA or a low dose of SEMA showed NAS reduction beyond 1 stage. A strong decrease in liver triglycerides (−56%), in the number of inflammatory foci (−59%) and in plasma ALT (−60%), was also observed in the ELA/SEMA arm, corroborating the effect on liver histology. Fibrosis improvement was observed in 29% of animals that received a low dose of ELA. SEMA showed no effect on fibrosis and did not enhance the ELA-induced change when used in combination.
A profound liver transcriptome remodeling was documented. A set of 2194 genes was differentially modulated in the ELA/SEMA combo arm vs 1140 and 55 genes in ELA and SEMA monotherapy arms, respectively. Surprisingly, SEMA treatment only modestly affected the expression of lipid-metabolism-related genes. However, numerous inflammatory genes and especially myeloid cell markers were selectively reduced in animals that received the combination. Further analyses to better characterize ELA/SEMA combo-induced changes in inflammatory infiltrate signature will be presented. In vitro studies to evaluate the direct signaling of both drugs on different myeloid cell populations will be also reported.
Conclusion: Combination of low doses of elafibranor and semaglutide alleviates severe NASH phenotype and liver injury markers in AMLN diet-induced disease model. Transcriptomic studies reveal that ELA and SEMA synergize to specifically reduce the inflammatory infiltration in the liver.

AS015

Therapeutic effect of a novel long-acting GLP-1/GIP/glucagon triple agonist (HM15211) in animal models of NASH and fibrosis

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Background and Aims: Nonalcoholic steatohepatitis (NASH) and fibrosis remains a major cause of liver-related mortality. However, no pharmacologic treatment has been approved despite accelerated drug development. Since multiple biological pathways are involved in disease progression, therapeutic approaches simultaneously targeting multiple pathways might be required to effectively treat NASH and fibrosis. To address this, we developed a novel long-acting GLP-1/GIP/Glucagon triple agonist, HM15211. Previously, HM15211 significantly improved steatosis, hepatic inflammation, and fibrosis in diet-induced NASH mouse models of NASH. Here, we further evaluated the anti-inflammation and anti-fibrotic effects in additional animal models of NASH and fibrosis.
Method: NASH and fibrosis mouse model was established by AMLN diet and thioacetamide treatment (AMLN/TAA mice) for 16 weeks, and HM15211 was subcutaneously administered during last 8 weeks. For direct anti-fibrotic effect evaluation, bile duct ligation (BDL)-induced fibrosis mouse model was established, and HM15211 was

administered for 2 weeks. At the end of treatment, the degree of fibrosis was evaluated by hydroxyproline (HP) contents and sirius red staining. Liver tissue samples were subjected to qPCR to determine the expression of relevant markers for inflammation and fibrosis, and blood levels of fibrosis surrogate markers were measured by ELISA.
Results: In AMLN/TAA mice, HM15211 treatment significantly reduced HP content (−53.1% *vs.* Veh.). In addition, the expression of markers for hepatic inflammation (−92.8, −34.7 and −32.7% *vs.* Veh. for F4/80, MCP-1, and IL-6) and fibrosis (−53.9, −41.4, and −51.9% *vs.* Veh. for alpha-SMA, TIMP-1, and collagen1a1) was significantly reduced in HM15211 treated group. Similar reduction in blood levels of TIMP-1, PIIINP and hyaluronic acid (HA) (−49.3, −48.0, and −49.1% *vs.* Veh., respectively) was also observed. In BDL model, HM15211 treatment showed greater reduction in HP content (−33.4 ~ −43.7% and −21.9% *vs.* Veh for HM15211 and OCA), and fibrosis score (1.0, 1.75, and 1.7 for HM15211, OCA and vehicle) compared to obeticholic acid (OCA). Consistently, blood levels of TGF-beta, HA, and TIMP-1 were also significantly reduced by HM15211 treatment.
Conclusion: Based on the beneficial effects in AMLN/TAA and BDL mice, HM15211 may provide therapeutic effects on fibrosis as well as NASH. Human efficacy studies are ongoing to assess the clinical relevance of these findings.

AS016
Combination therapy with a dual CCR2/CCR5 antagonist and a FGF21 analogue synergizes in ameliorating steatohepatitis and fibrosis

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Background and Aims: With new drug targets emerging, combination therapies appear attractive to treat NASH and fibrosis. Dual chemokine receptor types 2 and 5 (CCR2/5) antagonists can improve fibrosis by reducing monocyte infiltration and altering macrophage subsets in the liver. Fibroblast growth factor 21 (FGF21) is a non-mitogenic hormone that is a key regulator of lipid and glucose metabolism. A PEGylated FGF21 analogue has been shown to improve steatosis, liver injury and fibrosis markers in NASH patients. We compared effects of combined therapy to single drug treatment in mouse models of acute and chronic liver injury.
Method: We measured serum CCL2 in 85 patients with biopsy-proven NAFLD. We tested a CCR2/5 antagonist (BMS-687681, 45 mpk bid PO or 15 mpk bid in combination) and/or a PEG-FGF21 variant (PEG-FGF21v, BMS-986171, 0.6 mpk biw SC) in male C57BL/6J mice, subjected to either acute liver injury (single carbon tetrachloride injection, CCl_4) or chronic steatohepatitis and fibrosis (choline-deficient, L-amino acid-defined high-fat diet (CDAHFD) for up to 12 weeks).
Results: In NAFLD patients, CCL2 levels correlated with fibrosis severity. In acute liver injury, CCR2/5 antagonist treated mice had significantly lower numbers of circulating and hepatic $Ly6C^+$ inflammatory monocytes and monocyte-derived macrophages (MoMFs). Upon PEG-FGF21v treatment, hepatic MoMF numbers remained unaffected, but ALT and hepatocellular necrosis were reduced. In chronic steatohepatitis, compound dosing was initiated after 6w of CDAHFD, and effects were assessed after either short- (2w) or long-term (6w) treatment. In both regimens, CCR2/5 antagonism reduced MoMF, inflammatory markers and hepatic fibrosis, whereas PEG-FGF21v reduced body weight, liver triglycerides, steatosis, and NASH activity. Combination treatment demonstrated additive benefits of both therapies regarding weight gain, hepatic fat, ALT levels and fibrosis, while combination showed even synergistic effects on NAFLD activity score.
Conclusion: CCR2/5 antagonism blocks inflammatory monocytes infiltration, and treatment with an FGF21 analogue has beneficial effects on metabolism and pathogenic drivers of NASH and fibrosis. Combined therapy ameliorates progressive steatohepatitis and fibrosis more effectively than single drug treatment, corroborating the therapeutic potential of combining these two approaches in patients with advanced NASH.

AS017
A polygenic risk score for progressive non-alcoholic fatty liver disease risk stratification

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Background and Aims: Noninvasive identification of patients with dysmetabolism at risk of nonalcoholic fatty liver disease (NAFLD), severe fibrosis and hepatocellular carcinoma (HCC) is a major unmet clinical need. Genetic predisposition plays a major role in determining progressive NAFLD. We previously developed a genetic risk score (GRS) estimating the inherited predisposition to accumulate liver fat based on common variants in *PNPLA3*, *TM6SF2*, *MBOAT7* and *GCKR*. The aim of this study was to examine the accuracy of GRS to stratify the risk of NAFLD, severe fibrosis, and HCC in a multicenter cross-sectional cohort.
Method: We considered 2021 individuals: 464 without liver disease, 1034 with histological NAFLD without severe fibrosis, 275 with NAFLD and severe fibrosis without HCC, and 248 with NAFLD-HCC. All were genotyped for the rs738409 (*PNPLA3* I148M), rs58542926 (*TM6SF2* E167 K), rs641738 C > T at *MBOAT7* and rs1260326 (*GCKR* P446L). Genetic data were combined in the GRS, and association with disease risk was tested by multivariate logistic regression models, adjusted for age, sex, BMI, presence of diabetes (and fibrosis).
Results: In the overall cohort, GRS predicted NAFLD independently of confounders ($p < 10^{-11}$, OR for the upper quartile: 4.22, 95%CI 2.72–6.54), more robustly than the single variants. In patients with

NAFLD, GRS predicted severe fibrosis independently of confounders (p < 10^ −14, OR for the upper quartile 2.96, 95%CI 1.55–5.65), more robustly than the single variants, and the association was also independent of histological NASH. In NAFLD, GRS was also independently associated with HCC (p = 10^ −6, OR for the upper quartile 2.41, 95%CI 1.28–4.54). The AUROC was 0.604 for the GRS, better than the single variants alone. The association between GRS and HCC was independent of NASH, but it was lost after correction for fibrosis severity.

Conclusion: The polygenic GRS improved the accuracy to detect NAFLD, severe fibrosis and HCC compared to single variants. Genetically determined hepatic fat accumulation causes liver fibrosis. Although we could not rule out an independent contribution due to pleiotropic effects of specific variants, predisposition to HCC development seems mainly dependent on the induction of fibrosis. We are currently evaluating whether the GRS can improve the diagnostic accuracy of classical risk factors for NAFLD, severe fibrosis, and HCC.

AS018

Carbohydrate restriction reverses NAFLD by altering hepatic mitochondrial fluxes in humans

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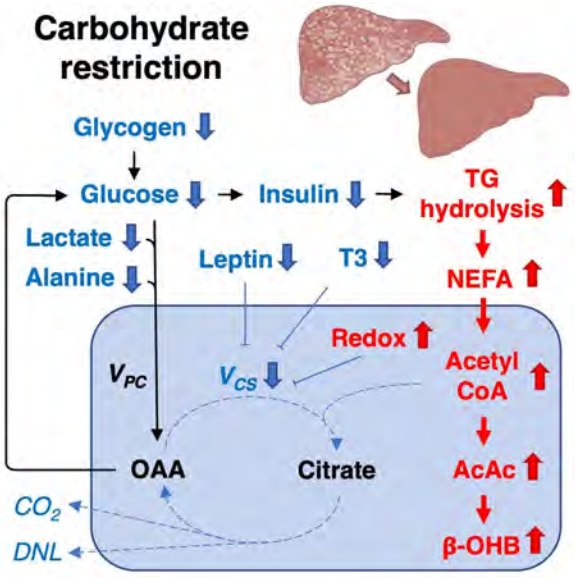
Background and Aims: Carbohydrate restriction (CR) has emerged as an effective dietary regimen in the management of non-alcoholic fatty liver disease (NAFLD), but the underlying intrahepatic mechanisms have remained poorly understood. We examined the mechanisms by which CR improves liver metabolism *in vivo* in humans before and after a 6-day CR diet using Positional Isotopomer NMR Tracer Analysis (PINTA) by infusing of [D_7]-glucose, [$^{13}C_4$]-hydroxybutyrate and [3-^{13}C]-lactate for quantification of rates of endogenous glucose production, ketogenesis and hepatic citrate synthase (V_{CS}) and pyruvate carboxylase (V_{PC}) fluxes.

Method: We performed PINTA in ten overweight/obese participants (mean age 58 ± 2 yrs, BMI 32 ± 2 kg/m^2, 50% men) before and after 6-day CR diet. Compliance was assessed by measuring plasma β-hydroxybutyrate and acetoacetate concentrations and by 3-day food records. Liver fat and stiffness were measured using magnetic resonance spectroscopy and magnetic resonance elastography. Potential regulators of V_{CS}, *i.e.* hepatic mitochondrial redox state (ratio of plasma β-hydroxybutyrate and acetoacetate) and plasma concentrations of leptin and triiodothyronine were also measured.

Results: The CR diet was very low in carbohydrates (183 ± 20 vs. 23 ± 1 g/day, before vs. during the diet, $p < 0.000001$) while intakes of other macronutrients were unchanged, which resulted in decreased energy intake (2019 ± 177 vs. 1444 kcal/day, $p < 0.01$). Plasma β-hydroxybutyrate and acetoacetate concentrations increased by 10-fold and 6-fold, and body weight decreased by 3% during the diet (all $p < 0.001$). The CR diet markedly decreased rates of endogenous glucose production (−22%), serum insulin concentrations (−53%) and liver fat content (−31%, all p < 0.001). The latter was attributed to increased mobilization of fatty acids (+35%), increased rates of ketogenesis (+232%), and decreased rates of V_{CS} (−38%, all p < 0.001) which together with reduced serum insulin concentrations limits hepatic lipogenesis. Reduced hepatic V_{CS} was associated with increased mitochondrial redox state as determined by ratio of plasma β-hydroxybutyrate and acetoacetate (+167%) and decreased plasma leptin (−45%) and triiodothyronine (−21%) concentrations.



Conclusion: We demonstrate heretofore undescribed mechanisms by which carbohydrate restriction reverses NAFLD in humans, *i.e.* by altering hepatic mitochondrial fluxes to promote hepatic fatty acid disposal.

Liver tumour – Basic

AS019

TREM2 protects the liver against hepatocellular carcinoma through multifactorial protective mechanisms

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Background and Aims: Hepatocellular carcinoma (HCC) represents the 6th most common cancer world-wide and the 3rd cause of cancer-related mortality. HCCs arise in a background of chronic liver diseases where chronic inflammation and regeneration play a pivotal role. We have previously shown that the triggering receptor expressed on myeloid cells 2 (TREM2) protects the liver from hepatotoxic injury, via its negative regulation of toll-like receptor (TLR)-derived signalling in non-parenchymal liver cells. However, its role in liver cancer is still far from clear. Here, the role of TREM2 in hepatocarcinogenesis and liver regeneration was investigated.
Method: TREM2 expression was analysed in liver tissue of patients with HCC from 2 independent cohorts compared to control individuals. Wild type (WT) and *Trem2*$^{-/-}$ mice were subjected to experimental models of HCC and liver regeneration. *In vitro* studies with hepatic stellate cells (HSCs) and HCC spheroids were conducted.
Results: *TREM2* expression is increased in liver tissue of patients with HCC compared to normal liver tissue. Interestingly, TREM2 expression positively correlates with immune cell infiltration (macrophages, NKT cells, dendritic cells and B cells, among others) and activated HSC markers in human HCC tumours. In addition, *Trem2* expression was induced in the livers of mice subjected to DEN-induced carcinogenesis (a mouse model of HCC) and to partial hepatectomy (mouse model of liver regeneration). *Trem2*$^{-/-}$ mice developed more liver tumours after diethylnitrosamine (DEN) administration, which was associated with exacerbated liver damage, inflammation, oxidative stress and hepatocyte proliferation. Moreover, *Trem2*$^{-/-}$ livers showed increased hepatocyte proliferation and inflammation after partial hepatectomy. *Trem2*$^{-/-}$ mice also exhibited enhanced carcinogenesis in fibrosis-associated HCC models. Specifically, *Trem2*$^{-/-}$ mice displayed more small tumours after DEN + CCl4 injections and increased tumour volume after 40 weeks of TAA treatment. Administration of an anti-inflammatory diet blocked DEN-induced hepatocarcinogenesis in *Trem2*$^{-/-}$ mice. The supernatant of human hepatic stellate cells overexpressing TREM2 inhibits human HCC spheroid growth *in vitro*.
Conclusion: *TREM2* in non-parenchymal cells protects the liver from hepatocarcinogenesis, representing a novel promising therapeutic target.

AS020
Hepatic stellate cell autophagy promotes HCC progression via GDF15

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Background and Aims: Autophagy in hepatoma cells is supposed to promote the progression of cancer. However, the effect of autophagy in hepatic stellate cells (HSCs) on hepatocellular carcinoma (HCC) has not yet been clarified.
Method: HepG2 cells and HuH7 cells were used as human hepatoma cells and LX-2 cells as human HSCs. Autophagy was examined from the ratio of the fluorescence intensities of GFP and RFP using LX-2 cells overexpressing GFP-LC3-RFP-LC3ΔG probe. Atg7 knockout or GDF15 knockout LX-2 cells were generated by CRISPR Cas9. HSC-specific Atg7 knockout (G-Atg7 KO mice) mice were generated by crossing GFAP-Cre mice and Atg7 fl/fl mice. These mice were administered streptozotocin at the age of 2 days, followed by a high-fat diet feeding. Human HCC samples were analyzed by single-cell RNA sequence (scRNAseq).
Results: When co-culturing LX-2 cells with hepatoma cells, autophagy in LX-2 cells was promoted, and cell viability in hepatoma cells was increased. Atg7 knockout in LX-2 cells attenuated the proliferation effect on hepatoma cells when co-culturing. HepG2 cells, but not LX2 cells, were successfully engrafted into NOG mice. The growth of xenograft tumor of HepG2 cells in NOG mice was accelerated by co-transplantation with LX-2 cells. The acceleration was suppressed by Atg7 KO in LX-2 cells. Wild-type (WT) mice or G-Atg7 KO mice were administrated with streptozotocin and fed a high-fat diet. Atg7 was efficiently inhibited in stellate cells isolated from G-Atg7 KO mice. At 20 weeks of age, there was no significant difference in body weight, adipose tissue weight, blood glucose level, serum ALT and insulin levels between them. The macroscopic tumor formation rate was lower in G-Atg7 KO mice than WT mice. The maximum size of liver tumors was significantly suppressed in G-Atg7 KO mice (2.0 ± 2.1 mm v.s. 10.0 ± 5.8 mm (p = 0.002)) with decrease in ASMA positive cells in tumor lesions. The number of liver tumors was also significantly suppressed in G-Atg7 KO mice. To examine the mechanism by which HSC autophagy promotes HCC growth, RNA expression was analyzed by RNA sequence after co-culturing. It revealed several genes expression levels significantly elevated in LX-2 cells co-cultured with HepG2 cells. Among them, GDF15 changed most drastically, and that was attenuated by Atg7 knockout in LX-2 cells. The concentration of GDF15 in supernatant of co-culturing cells was higher than that of mono-culturing LX-2 cells or HepG2 cells. GDF15 knockout in LX-2 cells attenuated the proliferation effect on HepG2 cells in co-culturing and xenograft model. In clinical specimens, serum GDF15 concentration correlated with the prognosis of HCC patients and scRNAseq showed that HSCs existed in HCCs and HSCs in tumorous lesion expressed GDF15 more than HSCs in non-tumorous lesion.
Conclusion: HCC promotes autophagy in HSCs, which modulates secreted proteins such as GDF15, leading to progression of HCCs.

AS021
Phospholipid metabolism rewiring in liver regeneration and hepatocellular carcinoma

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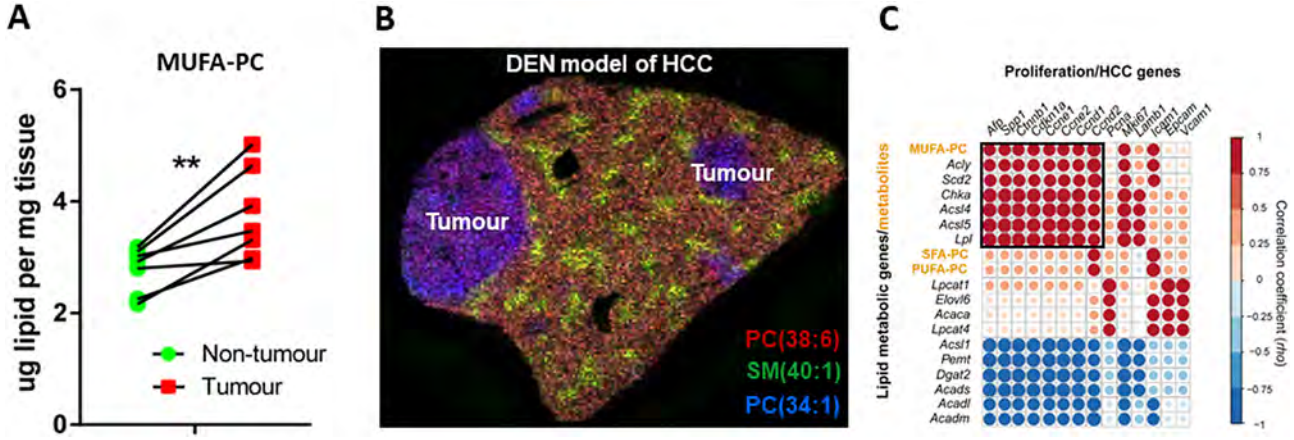
Background and Aims: Hepatocytes undergo profound metabolic rewiring when primed to proliferate during compensatory regeneration. Aberrant hepatocyte proliferation in chronic liver disease is also a driving cause of hepatocellular carcinoma (HCC), one of the leading causes of cancer-related deaths world-wide. Characterising the metabolic remodelling occurring in hepatocytes undergoing compensatory regeneration and in HCC is a crucial step to identify metabolic pathways that relate to cell proliferation in general and, more specifically, to hepatocellular carcinogenesis.
Method: In order to capture the metabolic signature of proliferating hepatocytes, we applied state-of-the-art systems biology approaches to models of liver regeneration (partial hepatectomy and acute carbon tetrachloride models), pharmacologically-(phenobarbital) and genetically (c-Myc inducible)-activated cell proliferation, and both mouse (DEN) and human HCC (on a fatty liver background). We integrated metabolomics, lipidomics and transcriptomics data, performed metabolic flux analysis and used mass spectrometry imaging (MSI) to study metabolic remodelling.
Results: An increase in monounsaturated fatty acid (MUFA)-containing phosphatidylcholine (PC) was measured by lipidomics in all the models (Fig. 1A), and confirmed by MSI in HCC (Fig. 1B). We integrated data from lipidomics, metabolomics and transcriptomics to link these changes in lipid content to lipid metabolism pathways. These included increased lipogenesis, fatty acyl desaturation and de novo synthesis of PC, as well as decreased beta-oxidation. We confirm this altered lipid signature in human HCC and show a strong positive correlation of MUFA-PC with key genes involved in proliferation and



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cell cycle control, as well as with other known genetic markers of hepatocellular carcinogenesis (Fig. 1C).
Conclusion: Overall, we demonstrate that lipid metabolic pathways are coherently altered, when hepatocytes switch to proliferation in murine and human models of compensatory regeneration and HCC. Hepatic MUFA-PC content closely correlates with markers of proliferation and hepatocellular carcinogenesis. We thus speculate that MUFA-PC and lipid imaging have the potential to offer new diagnostic and prognostic strategies for HCC. Our results also represent a source of targets for the development of new therapeutic strategies.

AS022
Dual inhibition of DNA methyltransferase 1 and the histone methyltransferase G9a as a new therapeutic strategy in hepatoblastoma

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Background and Aims: Hepatoblastoma (HB) is the most frequent pediatric tumor affecting the liver and albeit a rare tumor its incidence has increased four-fold in the past few decades. Surgical resection forms the mainstay treatment which frequently is preceded by neoadjuvant chemotherapy (cisplatin or doxorubicin). There is a significant proportion of patients (30%) presenting with advanced disease or more aggressive and chemoresistant variants with very poor prognosis. Molecularly, HB presents a surprisingly low mutation rate and very few genetic alterations, suggesting that epigenetic dysregulation plays a key role in HB development and progression. In the present work we have evaluated the functional relevance of the epigenetic complex constituted by DNA methyltransferase 1 (DNMT1), the histone methyltransferase G9a and the adapter molecule UHRF1 in HB and evaluated the *in vitro* therapeutic efficacy of a first-in-class substrate-competitive dual G9a-DNMT1 inhibitor.
Method: G9a, DNMT1 and UHRF1 mRNA levels were examined in a molecularly well-characterized set of HB samples (n = 32) and non-tumor tissues (n = 18) by qPCR. Anti-HB efficacy of our G9a/DNMT1 inhibitor lead compound, CM272, was tested in HepG2 and HuH6 cells, and in a unique collection of patient-derived HB cell lines, alone and in combination with cisplatin. Transcriptomic studies and epigenetic analyses of DNA and H3K9 methylation on selected genes were performed.
Results: A significant and correlative overexpression of G9a, DNMT1 and UHRF1 was observed in HB samples in association with poor prognosis. All cell lines showed very high sensitivity to CM272 (GI_{50}: 100–300nM). Mechanistically, there was a robust reinduction of tumor suppressor genes silenced in HB, such as HHIP, SFRP1, IGFBP3 or RASSF1A as well as a drastic decrease in the expression of genes involved in key metabolic pathways for tumor progression, such as HK-II, PKM2, LDHA or PHGDH. DNA hypermethylation and H3K9me2 levels at RASFF1A promoter were reduced upon CM272 treatment. CM272 significantly sensitized HB cells to cisplatin.
Conclusion: The epigenetic complex G9a-DNMT1-UHRF1 plays an important role in HB. Its pharmacological targeting with a dual inhibitor like CM272 can be promising antitumor strategy alone or in combination with current chemotherapeutic agents.

AS023
Analysis and prediction of cholangiocarcinoma from transcriptomic profile of patients

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Background and Aims: Cholangiocarcinoma (CCA) is the second most common type of primary malignancies of the liver after Hepatocellular carcinoma (HCC), accounts for 15–20% of liver cancer cases. Earlier, numerous studies mainly focussed on the identification of signatures and drug-targets for HCC; while only limited attempts made to scrutinize signatures for CCA. Previously, it has been shown that CCA and HCC have different carcinogenic mechanisms using metabolomic and transcriptomic profiles of ten HCC and six CCA patients. Thus, HCC biomarkers cannot be employed for CCA diagnosis. Thus, the recognition of CCA-specific transcriptomic signatures is vital for accurate CCA diagnosis. Hence, the current study is an attempt to fill this lacuna.
Method: Eight datasets containing a total of 350 CCA, 133 adjacent-non-tumorous and 90 HCC samples, were downloaded from GEO. Six

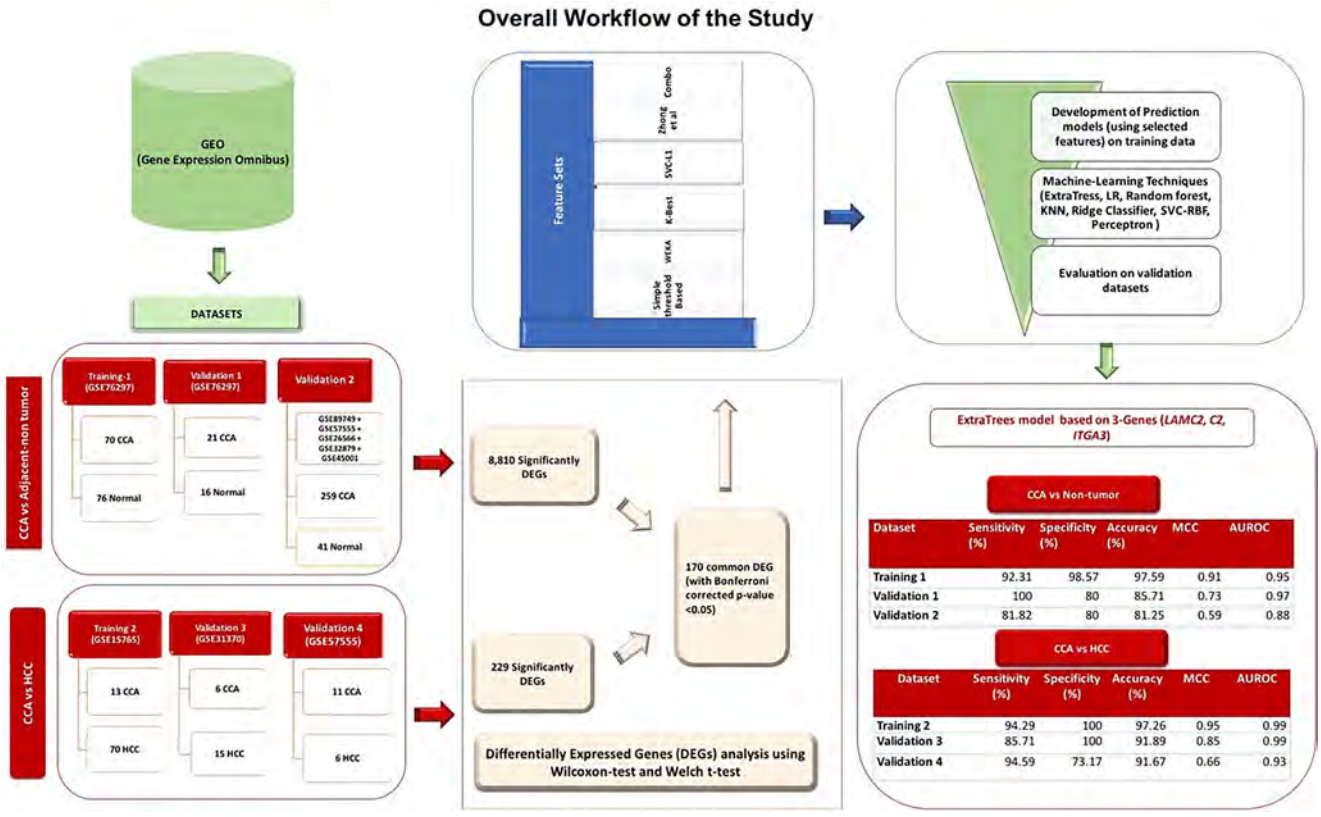

Figure: (abstract: AS023)

and three datasets used for CCA vs. non-tumorous and CCA vs. HCC analysis, respectively. Datasets partitioned into training and validation datasets, subsequently, pre-processed to apply statistical and bioinformatics analysis. Differentially Expressed Genes (DEGs) with Bonferroni-corrected p-value<0.05, identified by applying Wilcoxon and Welch t-test. Further, a Simple threshold-based approach, SVC-L1, *etc*. were used to select a signature-set with the minimum number of genes. Thereafter, several prediction models developed employing training dataset based on selected signature sets using different machine-learning techniques. Eventually, the performance is evaluated on validation datasets.

Results: Firstly, 170 common significantly DEG identified between CCA vs. non-tumorous and CCA vs. HCC samples. Subsequently, various machine-learning prediction models developed using different combinations of selected genes. ExtraTrees model based on three genes (*LAMC2, C2, ITGA3*) classified CCA from non-tumorous samples of the training dataset with accuracy 97.26% and AUROC 0.99, while, predicted samples of validation datasets with the accuracy of ~ 91% and AUROC 0.93–0.99. In addition, ExtraTrees model based on these three-genes categorized CCA from HCC samples of training dataset with an accuracy of 97.59% and AUROC 0.95, and of validation datasets with an accuracy of 81.25–85.71% and AUROC 0.88–0.97, respectively.

Conclusion: Prediction models developed based on three genes categorized CCA with high precision. Thus, they can be further explored for their diagnostic and therapeutic potential for CCA.

AS024

Single cell RNA sequencing and functional in vivo genetic manipulation reveal heterogeneity and tumor-promoting roles of cancer-associated fibroblasts in intrahepatic cholangiocarcinoma

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Background and Aims: Intrahepatic cholangiocarcinoma (ICC) is a desmoplastic tumor with abundant cancer-associated fibroblasts (CAF). With limited therapeutic options, there is growing interest in targeting CAF in ICC. Studies in other tumors have shown that CAF may promote or restrict tumor growth, possibly related to tumor or CAF heterogeneity. In ICC, CAF functions and heterogeneity remain largely unknown. Here, we aimed to dissect cellular origin, diversity and functions of CAF in ICC by single cell RNA-sequencing (scRNA-seq), and by *in vivo* CAF depletion or Cre-lox-based genetic CAF tracing and manipulation.

Method: ICC was induced by sleeping beauty-mediated expression of pT3-myrAKT-HA and pT3-YAP127SA or pT3-KrasG12D and Crisp/Cas sg-p19 by hydrodynamic injection. CAF origin and heterogeneity were analyzed in mice expressing Col1a1-GFP (labeling all CAF); LratCre and TdTom reporter (labeling hepatic stellate cells = HSC), and

by scRNA-seq using 10x Genomics. CAF functions were studied by CAF depletion in LratCre x iDTR or aSMA-TK mice, and by HSC-selective knockout of several ECM members including Col1a1, Wnts, RelA and growth factors via LratCre. Ki67, cleaved caspase 3 and CD3 were analyzed by IHC.

Results: LratCre tracing as well as scRNA-seq in 2 ICC models with different mutation profiles, showed that HSC contribute >85% of CAF. scRNAseq revealed multiple CAF subpopulations, including inflammatory (iCAF, 43%), myofibroblastic (myCAF, 36%), antigen-presenting CAF (apCAF, 2%) and mixed-marker CAF (19%). HSC markers segregated with iCAF and myCAF populations, whereas portal fibroblasts markers segregated with apCAF. Genetic CAF depletion strongly reduced ICC growth, mediated by reduced proliferation and increased apoptosis but not by CD3+ T cell infiltration. Deleting Col1a1 by LratCre (constitutive) or MxCre (inducible) reduced liver stiffness but did not reduce tumor growth. scRNA-seq revealed distinct candidates in myCAF and iCAF, suggesting a tumor-promoting role of specific ECM components in myCAF and growth factors in iCAF, which was functionally confirmed by *in vivo* studies.

Conclusion: Our data unveil CAF heterogeneity in ICC and show a tumor-promoting role of HSC-derived-CAF. Tumor promotion is mediated by iCAF and myCAF through distinct mediators. Surprisingly, type I collagen and stiffness do not contribute to the growth of this highly desmoplastic tumor. In summary, our studies point towards CAF as a novel therapeutic target in ICC.

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General session II and award ceremony I

GS08

Introduction of "reflex" AST testing in primary care increases detection of advanced liver disease: the Gwent AST project (GAP)

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Background and Aims: The incidence and mortality from chronic liver disease in the general population continues to increase. Previous studies have suggested that abnormal liver blood tests are frequently not followed up in primary care and historical clinical practice based on societal has not routinely incorporated assertive fibrosis testing although the recent BSG abnormal liver blood test guidance from 2017 aims to address this.
Method: In 2016 we set out to improve the recognition of significant liver disease through the reflex use of AST testing in the context of an elevated ALT. This work was commissioned by the Wales Liver Plan as a pilot, proof of concept service development pathway. This pathway Figure: facilitated automatic calculation of the AST:ALT ratio and advice to refer for further assessment (predominantly via Fibroscan) if the ratio was >1. We report here the 2 year experience of this pathway on the diagnosis of advanced fibrosis and cirrhosis.

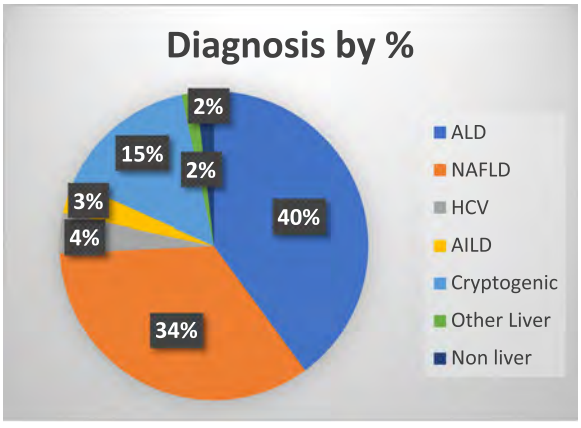

Figure: Clinical Diagnosis in Patients Undergoing Fibroscan.

Results: 17,770 individuals had an elevated ALT. Of these, 2,117 (12%) had an AST:ALT ratio >1. Of these patients, 750 were referred from primary care. 348 underwent Fibroscan. A significant number of patients (approximately 40%) did not attend (DNA) a Fibroscan appointment. In patients undergoing Fibroscan 43% had a reading <8 kPa, 28% were 8–15 kPa and 29% >15 kPa. The commonest cause of liver disease was NAFLD in 49% and Alcohol in 40% In total, 192 cases of advanced fibrosis were identified through this pathway and there has been an 81% increase in coded diagnoses of cirrhosis since its introduction. Furthermore, a further 33 patients who were not originally referred have subsequently received a liver diagnosis (28 with cirrhosis or HCC).
A FIB 4 score was calculable in 13,626 individuals and was >1.3 in 47% which would potentially lead to a 4 fold increase in secondary testing compared with an AST:ALT ratio >1.
Conclusion: Introduction of reflex AST testing and calculation of the AST:ALT ratio in primary care has led to a significant increase in new diagnoses of cirrhosis. However, GP compliance with the pathway was low and further work is required to improve this as well as providing better community access to Fibroscan testing to reduce the DNA rate. Future work will also explore the utility of reducing the AST: ALT threshold to 0.8 as some cases of advanced fibrosis may have been missed by utilising the higher threshold.

GS09

Monoacylglycerol lipase reprograms lipid metabolism in macrophages and hepatocytes to promote liver regeneration

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Background and Aims: Monoacylglycerol lipase (MAGL) is a proinflammatory enzyme that reprograms lipid metabolism by converting monoacylglycerols into free fatty acids, in particular arachidonic acid. We have previously shown that MAGL displays pro-inflammatory and profibrogenic functions in the liver. Since a delicate balance exists between regeneration and fibrosis, and because both parenchymal and non-parenchymal cells participate to tissue repair, in the present study we studied the impact of MAGL on liver regeneration, and investigated the respective contribution of hepatocytes and immune cells.
Method: Liver regeneration was induced by 2/3 partial hepatectomy (PH) or acute intraperitoneal injection of carbon tetrachloride (CCl_4). Mice with genetic ($MAGL^{-/-}$) or pharmacological (using MJN110) invalidation of MAGL were used, as well as mice bearing MAGL invalidation in myeloid cells ($MAGL^{Mye-/-}$), lymphocytes ($MAGL^{Lympho-/-}$) or hepatocytes ($MAGL^{Hep-/-}$), and their control counterparts (WT). *In vitro* studies were conducted on bone marrow derived macrophages (BMDM) and primary hepatocytes.
Results: Mice with global invalidation of MAGL, or exposed to the pharmacological MAGL inhibitor MJN 110 showed impaired liver regeneration following PH or acute injection of CCl_4, reflected by a lower number of BrdU+ hepatocytes and reduced Cyclin A expression. MAGL global inhibition was associated with a lower production of PGE2 and reduced mRNA expression of TGF-α, IL-17 and HGF after injury. A similar impairment of liver regeneration was also observed in mice bearing a specific MAGL deletion in hepatocytes or in myeloid cells. In $MAGL^{Mye-/-}$ mice, liver regeneration defect was associated

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with a decrease in hepatic TNF production. Mice with MAGL deletion in lymphocytes showed similar hepatocyte proliferation than WT counterparts.
In vitro studies further confirmed that primary hepatocytes exposed to MJN110 or isolated from $MAGL^{-/-}$ mice displayed lower proliferative index compared to control hepatocytes, and decreased PGE2 production. Finally, LPS-stimulated BMDM isolated from $MAGL^{Mye-/-}$ mice or from wild type mice but exposed to MJN110 displayed reduced TNF secretion compared to their respective control.
Conclusion: Inhibition of MAGL is associated with compromised liver regeneration, that results both from a direct effect on hepatocytes and an indirect effect on macrophages Thus, while being profibrogenic, MAGL displays pro-regenerative capacities in the liver.

GS10

Short-term treatment with RNA interference therapy, JNJ-3989, results in sustained hepatitis B surface antigen supression in patients with chronic hepatitis B receiving nucleos(t)ide analogue treatment

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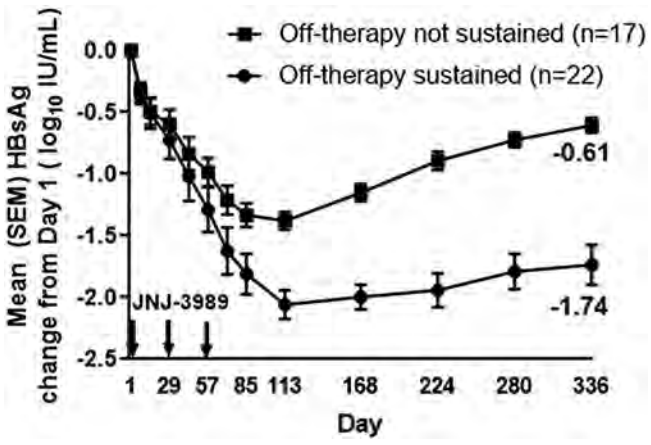
Background and Aims: RNA interference (RNAi) therapy with JNJ-3989 silences HBV RNA transcripts from episomal cccDNA and integrated HBV DNA. In AROHBV1001 (phase 2a), JNJ-3989 (3 monthly doses 25–400 mg) + a nucleos(t)ide analogue (NA) demonstrated antiviral activity in patients (pts) with chronic hepatitis B (CHB) by reducing serum viral parameters (AASLD 2019). 9-month follow-up data for pts on ≥100 mg are presented.
Method: 8 CHB pts/cohort (NA experienced or naïve; HBeAg +ve or –ve) received 3 subcutaneous JNJ-3989 doses (days 1, 27, 57) of 100, 200, 300 (n = 16) or 400 mg. Pts started/continued with an NA on day 1 and continued throughout the study. Safety and viral parameters (HBsAg, HBeAg, HBV DNA, HBV RNA, HBcrAg) were assessed. For all parameters, sustained suppression was defined as a ≥1.0 $\log_{10}$ reduction from day 1 or a value <lower limit of quantification at day 336.
Results: 40 pts were enrolled: 73% males; 85% Asian; median age 45 (26–66) yrs; HBeAg: 14 +ve, 26 –ve; 80% NA experienced. No deaths, treatment discontinuations or drug-related serious adverse events (AEs) were seen; 1 pt was lost to follow up. The most common drug-related AEs were mild injection site AEs (7 pts). One AE of elevated ALT (peak 136 U/L) was reported. HBsAg levels rapidly declined during treatment. At the HBsAg nadir, 39/40 pts had a ≥1.0 $\log_{10}$ HBsAg reduction from day 1; range 1.11–3.77; for 1 pt the maximum decline was 0.77 $\log_{10}$. Mean nadir for HBsAg (SE) $\log_{10}$ reduction from day 1 was 1.72 (0.18; 100 mg), 1.79 (0.14; 200 mg), 2.04 (0.20; 300 mg; 11/16 HBeAg +ve) and 1.90 (0.18; 400 mg). 22/39 (56%) pts had sustained HBsAg reductions (≥1.0 $\log_{10}$ reduction at day 336, ~9 months after last JNJ-3989 dose, Fig); mean (SE; range) HBsAg reductions in pts with sustained suppression were: 1.74 (0.77; 1.00–3.38) vs 0.61 (0.06; 0.15–0.96) for non-sustained suppression. For pts with quantifiable parameters on day 1 and available data at day 336, a sustained suppression was observed for HBV RNA in 15/26, HBeAg in 9/14 and HBcrAg in 10/24 pts.



Conclusion: JNJ-3989 (100–400 mg) with an NA was well tolerated in CHB pts. A ≥1.0 $\log_{10}$ reduction in HBsAg at nadir was achieved in 98% of pts. A subset of pts had sustained suppression of HBsAg ~9 months after the last RNAi dose (mean 1.74); sustained suppression of other viral parameters was also seen. Studies with longer term dual therapy (48 weeks) and triple therapy including a capsid assembly modulator are underway.

GS11

Macrophage scavenger receptor 1 mediates lipid-induced inflammation in human obesity-related non-alcoholic fatty liver disease

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Background and Aims: Although low-grade chronic hepatic inflammation (steatohepatitis) plays a key role in the pathogenesis of NAFLD, there is substantial inter-patient variation in its occurrence and the molecular regulators controlling obesity-associated

inflammation and consequent disease progression remain incompletely defined. Recent data showed that pro-inflammatory activation of macrophages by saturated fatty acids is independent of Toll-like receptor 4, yet the receptor that is responsible is still not known. In this study we aim to investigate the role of the phagocytic receptor, macrophage scavenger receptor 1 (MSR1, also known as SR-A or CD204), in NAFLD by combing human transcriptomic and genetic data with transgenic mouse models and *in vitro* assays.

Method: For the histopathological and transcriptomics nanoString® study, 214 liver and adipose tissue samples from Caucasian patients were included. For the Genome Wide Association Study, 1,483 patients with histological proven NAFLD were included recruited at different European centres. Quantitative trait analysis was done using the UKBiobank cohort. *Msr1*$^{-/-}$ and Wt mice were fed or high-fat and high-cholesterol diet. Tissue-specific macrophages were isolated using magnetic beads or FACS; bone marrow-derived macrophages (BMDMs) were co-cultured with or adipocyte-like or hepatoma cells in the presence of lipids. Read-out was based on histological and biochemical results, Seahorse and mass-spectrometry.

Results: We show that MSR1 expression in the liver of human NAFLD patients is associated with a greater disease activity and the occurrence of hepatic lipid-laden foamy macrophages. Mice lacking Msr1 are protected against diet-induced metabolic disorder, showing less hepatic inflammation and fibrosis, reduced circulating fatty acids, hepatic triglycerides levels and more lipid storage in the adipocytes. Moreover, MSR1 triggers the inflammatory activation of liver macrophages *in vivo* and *in vitro* in the presence of lipids in a JNK-dependent manner. We further demonstrate that MSR1 induces lipid-induced inflammation independent of lipopolysaccharide. Using a cohort of 1,483 European Caucasian patients with histologically-proven NAFLD and 17,781 European general-population controls, we identified 4 SNPs at the *MSR1* locus with a p-value<5*10^{-4}, with rs41505344 as the most significant. Quantitative trait analysis for rs41505344 in 430,101 patients enrolled in the UKBiobank showed a significant correlation with serum triglycerides and ALT levels.

Conclusion: Our data suggest a critical role for MSR1 as a sensor for lipid homeostasis and a potential therapeutic target for the treatment of NAFLD.

GS12

Long-term patient and graft survival after liver transplantation for autoimmune hepatitis

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Background and Aims: Autoimmune hepatitis (AIH) is an autoimmune liver disease requiring liver transplantation (LT) in a subgroup of patients (AIH-LT). In these patients, data on long-term outcomes is scarce. The aim of this study was to assess long-term patient and graft survival after AIH-LT from the prospective multicentric European Liver Transplant Registry (ELTR).

Method: The ELTR database was screened for patients who received AIH-LT between 1998 and 2017. In total, n = 2,515 patients were identified and included in the analysis. As controls, patients were included who underwent LT during the same time as a consequence of the other autoimmune liver diseases primary biliary cholangitis (PBC-LT, n = 3,733) and primary sclerosing cholangitis (PSC-LT, n = 5,155), and for alcoholic liver cirrhosis (ALC-LT, n = 19,567). Survival was analyzed using the Kaplan-Meyer method and Cox proportional hazards regression.

Results: AIH-LT resulted in an actuarial patient survival of 79.4%, 70.9% and 60.6% and an actuarial graft survival of 73.2%, 63.4% and

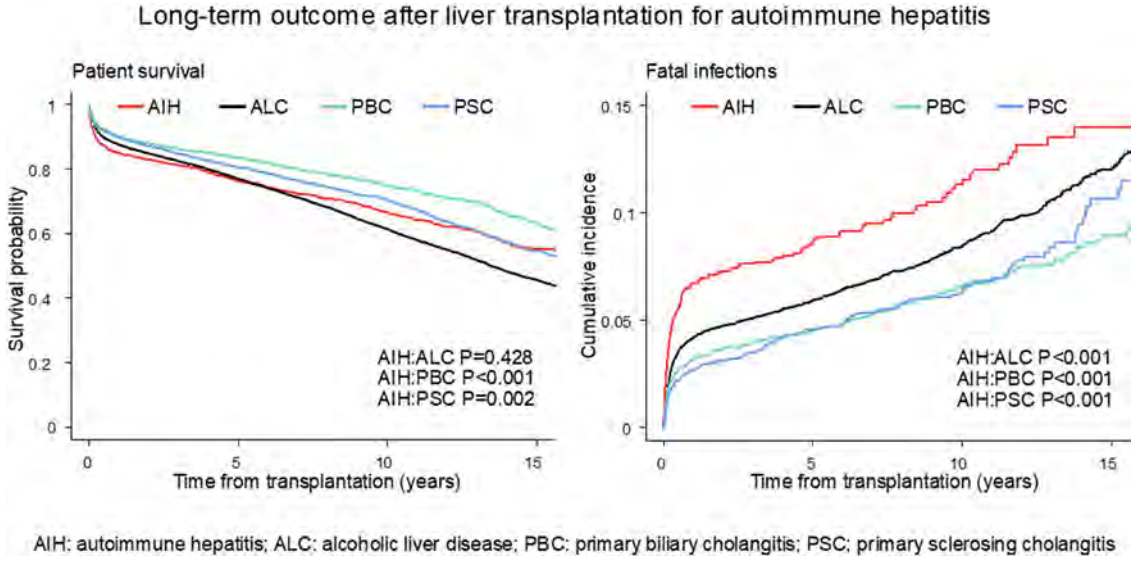

Figure: (abstract: GS12)

50.9% after 5, 10 and 15 years of follow-up, respectively. Overall survival of patients after AIH-LT was comparable to patients after ALC-LT ($p = 0.428$), but inferior compared to patients after PBC-LT (hazard ratio [HR] = 1.48, $p < 0.001$) and PSC-LT (HR = 1.18, $p = 0.002$). Patients after AIH-LT showed an increased risk of death within 5 years of follow-up compared to all other groups (HR = 1.13–1.56, $p \leq 0.031$). AIH-LT patients had an increased hazard of death (HR = 1.37–1.84, $p < 0.001$) and graft loss (HR = 1.38–1.88, $p \leq 0.002$) as a consequence of infections. In particular, patients after AIH-LT showed a greatly increased risk for lethal fungal infections (HR = 3.24–4.02, $p < 0.01$). All deaths from fungal infections affecting AIH-LT patients occurred during the first year of follow-up. Patients with AIH receiving a living donor LT showed a decreased survival compared to AIH-LT patients who received donation after brain death (HR = 1.93, $p = 0.001$).
Conclusion: Survival of patients after AIH-LT was inferior compared to all other patient groups within the first 5 years after LT. This was mainly explained by an increased incidence of early lethal infections, including fungal infections. After 5 years of follow-up the prognosis of patients after AIH-LT improved considerably compared to the control groups.

GS13
Profiling of routine serum parameters and AFP evolution in cirrhosis following HCV eradication for stratification of HCC risk: a trajectory clustering analysis from the ANRS CO12 CirVir cohort
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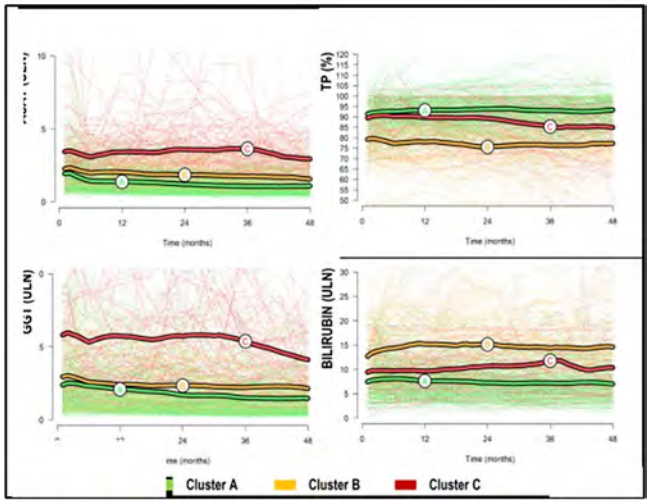
Background and Aims: HCC surveillance following HCV eradication in patients with cirrhosis needs to be refined to tailor personalized management and increase cost-effectiveness. Our study aimed to identify specific longitudinal profiles of routine serum parameters (RSP) and AFP evolution before and after HCV eradication in patients with cirrhosis which could be associated with higher risk of HCC occurrence.
Method: Data were driven from the French ANRS CirVir multicenter prospective cohort of patients with biopsy-proven viral compensated cirrhosis included in semi-annual HCC surveillance programs. Serum AFP and RSP (ALT, AST, GGT, PT, albumin, bilirubin, platelets) were assessed every 6 months. For the present analysis, only patients with at least 3 available AFP and RSP repeated measurements per trajectory analysis (i) no/before SVR, (ii) after SVR achievement) were included. Trajectory analysis was based on a k-means approach for clustering individuals with similar trajectories of AFP and RSP over time.
Results: After a median follow-up of 74.2 months, 717 patients with active HCV replication at baseline and 413 achieving SVR during follow-up were included, of whom 142 and 47 patients developed HCC, respectively. Before SVR achievement, trajectory analysis identified 3 clusters of patients with common AFP and RSP evolution, with profiles characterized by increasing AFP and the highest GGT/ALT/AST levels (cluster A, n = 190; HCC incidence during follow-up 25.3%), a globally worsening liver function (cluster B, n = 198; HCC 26.8%), or overall more favorable and stable levels over time (Cluster C, n = 329; HCC 12.5%, $p < 0.0001$). In the 413 patients who achieved SVR, trajectory analysis then revealed 3 post-SVR patients clusters (Figure), all demonstrating a global trend towards AST, ALT, GGT and AFP normalization, particularly in Cluster A (n = 228; HCC 7.5%). Of note, the two other clusters were associated with higher HCC incidence rates despite SVR achievement, being characterized either by persisting impaired liver function (cluster B, n = 109; HCC 15.6%) or elevated biochemical parameters (Cluster C, n = 95; HCC 13.7%).



Conclusion: Liver function impairment ("liver failure cluster") or persistent elevated biochemical parameters ("inflammatory cluster") despite SVR achievement in cirrhosis define two different profiles of patients in whom the residual risk of HCC following HCV eradication is increased. These analyses based on novel statistical approaches suggest that HCC surveillance in these patients could be refined and improved according to the longitudinal evolution of these parameters over time.

Nurses and AHP: Oral presentation

N01
Home based care pathway for the stratified treatment of HCV infection
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Background and Aims: Directly acting anti-viral agents (DAAs) for HCV infection have an excellent safety record and are suited for use in community environments which better meet patient needs. We present a novel home treatment pathway, delivered by a partnership between specialist hepatitis nurses and pharmacists in the Nottingham regional Hepatitis C Operational Delivery Network (ODN).
Method: Patients eligible for DAAs are assessed for suitability for homecare on the basis of: competence to adhere to therapy without direct supervision; no current or previous evidence of hepatic decompensation; contactable by telephone. Following signed consent, patients receive: one month medication; a schedule for community blood testing; information leaflets; hospital contacts. DAAs and blood forms are then delivered to the patient's home each month by pharmacy until completion. A dedicated pharmacy technician works with specialist hepatitis nurses and ODN Management to co-ordinate the service. 12 week post-treatment blood tests are organised by the technician and reviewed by specialist nurses.
Results: Since inception of the service in 2016, 261 patients have been treated at home. 85% of those offered the choice of home or

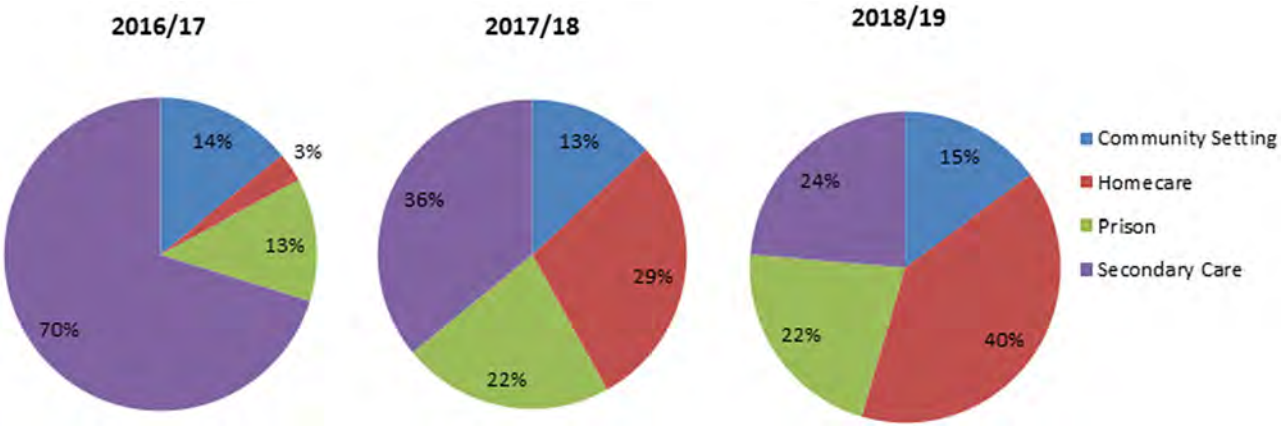

Figure: (abstract: N01): Percentages of patients treated in different healthcare settings in Nottingham annually between April 2016 and September 2019.

hospital based care during this period elected to receive treatment at home. Of those commenced on treatment, 234 have completed. Of the 179 with a 12 week post treatment test result, 177 achieved sustained viral response (SVR). The remainder have either not completed treatment or had a 12 weeks post treatment test. Six patients defaulted from treatment and four returned to hospital based care. Two patients died for reasons unrelated to treatment. 61 feedback forms have been returned with very positive feedback. The Homecare pathway was particularly valued by patients living distant from the hospital.

Conclusion: Homecare provides a safe and scaleable option preferred by patients. The strategy of pharmacy based implementation and economies of staff time intrinsic to the model has relieved pressure on specialised hepatitis services. Homecare has led a major and ongoing reduction in proportions of patients treated in secondary care (Figure 1). This has allowed the hospital to focus on patients with severe co-morbidities and the ODN to shift resources onto the community to promote case finding and community care for harder to reach groups with HCV infection.

N02

Oral health and the impact of oral diseases on the clinical course of cirrhosis

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Background and Aims: Poor oral health is prevalent in patients with cirrhosis, but the clinical significance is largely unknown. The aim of the study was to describe oral health and the prevalence of oral diseases in a cohort of cirrhosis patients, and to examine the association of oral diseases on the clinical course of cirrhosis.

Method: 184 consecutive cirrhosis patients were enrolled. They underwent a standardized oral clinical and radiographic examination. One-way anova was used to examine the association between single and multiple oral diseases and patients cirrhosis-related complications, inflammation- and nutritional status at baseline. Cox regression adjusted for confounding by age, male gender, smoker status, alcohol use, alcoholic cirrhosis, comorbidity, and MELD score was used to examine the associations between single and multiple oral diseases and the incidence of mortality.

Results: At baseline, the median number of teeth was 22 and 18% of the patients were edentulous. Twenty-seven percent had gross caries, 46% periapical lesions, 27% oral mucosal lesions, and 45% severe periodontitis. Sixty-one percent of the patients had one or more oral diseases. Having multiple oral diseases were associated with a gradual increase in cirrhosis-related complications (from 50.0% to 82.3%, p = 0.05), C-reactive protein (from 11.1 to 41.2 mg/L, p = 0.02), and nutritional risk score (from 3 to 4, p = 0.08). The total follow-up time was 427 years with a median of 2 years per patient and 66% of the patients died during follow-up. Multiple oral diseases were associated with higher cirrhosis-related mortality (HR 1.56, 95% CI 1.02–3.14, HR 1.91, 95% CI 1.12–3.24, and HR 4.51, 95% CI 1.30–15.62) in both the crude and adjusted analysis (Table 1).

Conclusion: The cirrhosis patients had poor oral health. The presence of multiple oral diseases was associated with a worsened clinical course of cirrhosis. The finding seems to necessitate closer attention to oral health in the clinic for patients with cirrhosis.

Table 1: (abstract: N02): Oral diseases and risk of all-cause and cirrhosis-related mortality

	All-cause mortality		Cirrhosis-related mortality	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
One oral disease vs. no oral disease	1.05 (0.67–1.66)	1.01 (0.53–1.36)	1.07 (0.64–1.79)	1.01 (0.52–1.53)
Two oral diseases vs. no oral disease	1.88 (1.17–3.03)*	1.54 (0.94–2.51)	1.48 (1.01–3.68)*	1.56 (1.02–3.14)*
Three oral diseases vs. no oral disease	1.37 (0.75–2.51)	1.55 (0.82–2.92)	2.20 (1.31–3.68)*	1.91 (1.12–3.24)*
Four oral diseases vs. no oral disease	2.09 (0.64–6.77)	2–35 (0.69–7.98)	3.15 (1.05–10.32)*	4.51 (1.30–15-62)*

Associations are expressed as hazards ratios (HR) with confidence intervals (CI), and presented without adjustment and with adjustment for age, gender, smoker status, alcohol use, alcoholic cirrhosis, comorbidity, and MELD score.
*$p < 0.05$.

N03

Empowerment of liver cancer patients for an improved management of post-embolization syndrome: impact of a nurses educational program

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Background and Aims: Chemoembolization (TACE) is the recommended treatment for hepatocellular carcinoma in the BCLC intermediate stage classification. The most frequent adverse events are fever, pain, nausea and fatigue known as "post-embolization syndrome (PES)." PES can cause anxiety and prompt consultations, unscheduled outpatient visits and emergency room attendance. The study evaluates how the BCLC Nurses Educational Program (BCLC-NEP) encourages patient autonomy after TACE to optimally manage PES.
Method: We retrospectively analyzed prospective data of all BCLC TACE-treated patients from Feb/2014 to Feb/2017. The program includes three key nurse visits: an outpatient visit before treatment, an inpatient visit post-procedure, and a 1-week-postTACE outpatient visit and phone consultations on request. This study analyzed symptoms reported after hospital discharge for the first two TACE sessions, and registered who resolved the first PES complaint reported by each patient.
Results: We reviewed 104 TACE-candidates: 92 TACE-treated patients who received at least the first TACE [median age 69 (range; 43–85), 85% male, (BCLC-A 46.7%, BCLC-B 53.3% and Child Pugh A (92.4%)]; 63 patients who received a 2nd TACE.
Seventy-nine patients (75.9%) reported PES after the first TACE, 52 (65.8%) were able to manage symptoms autonomously, 17 (21.5%) received nurse intervention and 8 (10.1%) required physician intervention. Patient interventions followed the BCLC-NEP recommendations regarding self-monitoring (50%), medication use (38.5) and other issues (7.6%). Only two patients (3.9%) attended the emergency department due to fever and pain. The main nurse intervention after TACE involved education and empowerment (88.2%).
After the second TACE, 50 patients (79.3%) reported PES, 39 (78%) were able to resolve the first sign/symptoms autonomously, 9 (18%) needed nurse intervention and 2 (4%) required physician intervention. Resolution of patient issues was achieved by following instructions regarding self-monitoring 46.2% and drug intake 53.8%. The main role of nurses after the second TACE was education (88.9%).
Conclusion: The BCLC-NEP for TACE patients promotes patient autonomy in PES management. The impact of the program proved more noticeable after the second TACE when patients had more experience with treatment and PES management (78%). This study reflects the extent to which the professional skills of nurses has an impact on the management of patients with liver cancer.

N04

Addition of palliative care nurse on the liver care team

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Background and Aims: Management of decompensated end stage liver disease (ESLD) individuals is a complex practice issue requiring collaboration between patients, caregivers, and a multidisciplinary team. Hospitalization is often required. Due to the uncertainty of prognosis and disease trajectory the role of palliative care in this population is not clearly understood. Providers often associate palliative care as "giving up" with removal of treatment modalities leading to a low rate of referrals to palliative care for these patients. Palliative care is an approach which is very distinct from end-of-life hospice programs. The goal of palliative care is to alleviate physical, psychosocial and spiritual suffering regardless of end-of-life. This provides complementary supportive services for seriously ill patients while pursuing aggressive, life-prolonging and curative care of chronic illness.
Method: In February 2018 a Palliative Care Nurse (PCN) was added to a specialized liver care team in a single center acute care hospital. The PCN joined daily rounds on all hospitalized ESLD patients and received referrals for one-on-one consultation. Consultation focused on supporting the care of these patients and their families in goal of care discussions, advance directives, and referrals for services as appropriate. Rates of referral for consultation as well as patient outcomes were captured. The EASL-CLIF scores were utilized to determine prognosis and trajectory of disease in these hospitalized patients.
Results: Between 02/2018 and 10/2019 there were 615 admissions with a diagnosis of ESLD with decompensation. Complication of portal hypertension such as ascites, variceal hemorrhage and hepatic encephalopathy was the most common reason for admission. The PCN provided 169 unique care consults to 89 ESLD patients during their acute care admissions. Patients determined to have ACLF Type 2 who were not transplant candidates were referred for palliative care, while the ACLF Type 3 patients were referred to a hospice program. All patients received Goals of Care discussion that included patient and family discussions of desired outcomes, advanced directives and/or care planning upon discharge. 29 patients (33%) were referred to Palliative Care; and 39 patients (43%) were referred to Hospice.
Conclusion: The need for palliative care in ESLD is increasing; although there are many barriers to the utilization of these services. The addition of a dedicated palliative care nurse to the acute care team caring for ESLD patients provides a mechanism to increase awareness of palliative care concepts, increase utilization of the concepts and overall improve patient and family quality of life, improve communication and goal setting, reduce suffering and impact appropriate referrals for needed services in a timely manner.

Acute liver failure

AS026

The VWF/ADAMTS13 unbalance, but not global coagulation or fibrinolytic status, is associated with outcome and bleeding in patients with acute liver failure

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Background and Aims: Patients with acute liver failure (ALF) rarely bleed, although historically they were considered to have a bleeding tendency. In fact, ALF is characterized by rebalanced hemostasis with hypercoagulable features, including an unbalance between the platelet adhesive protein Von Willebrand Factor (VWF) and its

cleaving protease, ADAMTS13, and a hypofibrinolytic status. Rodent models have shown a link between VWF, hepatic platelet accumulation, and progression of ALF. Here, we evaluated the hemostatic state of ALF patients in relation to bleeding and clinical outcome.
Method: Patients with ALF (INR (international normalized ratio) ≥1.5) or severe acute liver injury (ALI; INR ≥ 2.0) were recruited from the US ALF Study Group Registry between 2011 and 2018. Citrated plasma samples were taken on admission and levels of VWF, ADAMTS13 activity, thrombomodulin-modified thrombin generation, and clot lysis time were determined, and compared to levels in 40 healthy controls.
Results: We studied 676 patients, of whom 308 patients (45.6%) had acetaminophen-induced ALF. Bleeding occurred in 50 patients (7.4%), and 483 patients (71.4%) survived without liver transplantation (LT). ALF patients had 5-fold increased VWF levels, 5-fold decreased ADAMTS13 activity, similar thrombin generation, and 2.4-fold increased clot lysis time, compared to controls. Patients with bleeding complications had higher VWF levels (523% vs. 441%; p = 0.0122), and lower ADAMTS13 activity (15% vs. 22%; p = 0.005) compared to patients without bleeding. Thrombin generation and clot lysis time did not differ significantly between bleeding and non-bleeding patients. Patients who died or underwent LT within 21 days of admission had higher VWF levels (559% vs. 404%; p < 0.0001), lower ADAMTS13 activity (18% vs. 22%; p = 0.0111), similar total thrombin generation, and shorter clot lysis time (136 min vs. 146 min; p = 0.04), compared to transplant-free survivors.
Conclusion: Hemostasis in a large cohort of patients with ALF is characterized by VWF/ADAMTS13 unbalance, normocoagulability, and hypofibrinolysis, features which do not suggest a bleeding diathesis. The VWF/ADAMTS13 unbalance is associated with poor outcome, consistent with our recent studies suggesting a detrimental effect of VWF in ALF in mice. The association between VWF/ADAMTS13 unbalance and bleeding complications suggest that bleeding in ALF reflects the effects of systemic inflammation rather than coagulopathy.

AS027
Bicyclol mitigates acute liver injury via inhibition of ferroptosis by modulating GPx4/Xc- system activity

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Background and Aims: Acute liver injury (ALI) relates to high mortality rates globally, which is compromised with several patterns of programmed cell death (PCD) including necrosis, apoptosis as well as autophagic-dependent cell death. Ferroptosis is a recently discovered form of PCD characterized by iron-dependent accumulation of reactive oxygen species. Bicyclol, a novel synthetic anti-hepatitis drug, has been shown to protect against liver damage via various pharmacological activities. Our previous study has showed that bicyclol could enhance autophagy and suppress oxidative stress for alleviating carbon tetrachloride (CCl_4)-induced acute liver injury (ALI). However, the potential role of ferroptosis in ALI and the modulatory mechanism of bicyclol remains elusive and warrants further investigation.
Method: ALI was induced by CCl_4 treatment *in vivo* and *in vitro*. Hepatic damage was assessed via measuring serum concentration of ALT, and liver tissue was subjected to H&E staining for histological scoring. Expression of protein with respect to ferroptotic machinery was assessed by WB. Transmission electron microscopy was applied to investigate morphological change of mitochondria. The production of several damage-associated molecular pattern molecules (DAMPs) was determined by ELISA and qRT-PCR. The production of ferroptosis-related proteins was compared by WB in CCl_4-challenged HepG2 cells. The underlying molecular paradigms that regulate ferroptosis was confirmed by disruption of Gpx4 *in vitro*.
Results: Our *in vivo* model showed enhanced lipid peroxidation and labile iron accumulation with concomitant cell-death during CCl_4 exposure. Mice treated with bicyclol exhibited marked liver protection which was positively regulated by Gpx4 and system xc-, and these hepatoprotective impact were similar to administration of ferrostatin-1 (a specific inhibitor of ferroptosis). Meanwhile, NCOA4-mediated ferritin selective autophagy (ferritinophagy) was initiated during ferritin degradation in response to CCl_4 treatment, which was reversed by bicyclol pretreatment. Additionally, bicyclol could attenuate the increased expression of level of PTGS2 and its gene product cyclooxygenase-2 *ex vivo*.
Conclusion: These results implicate that ferroptosis may contribute to hepatic cytotoxicity during CCl_4 exposure, that bicyclol has protective potential via inhibition of ferroptosis and subsequent DAMPs release. The insight achieved from this result advances our knowledge of ALI relevant cell death cascade and be critical for future preclinical studies.

AS028
Safe and effective treatment of acute liver failure by allogeneic transplantation of stem cell-derived encapsulated liver tissue without immunosuppression

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Background and Aims: There is an urgent need for new therapies capable of replacing liver functions in patients with acute liver failure (ALF). We developed a human induced pluripotent stem cell (iPSC)-derived Encapsulated Liver Tissue (ELT) capable of consistently performing mature liver functions *in vitro* and *in vivo*. Thanks to the combination of complex iPSC-derived liver organoids and tailored biomaterials, the ELT performs liver-specific synthetic and metabolic functions at least as effectively as primary human hepatocytes, with the added advantages of being stable over time and upon cryopreservation, lot-to-lot consistency and sustainability (lower costs and unlimited availability). Here we assessed the efficacy and safety of the human ELT to treat ALF.
Methods: We generated human ELT using our patented, GMP-ready protocols, and transplanted them into immunocompetent mice with

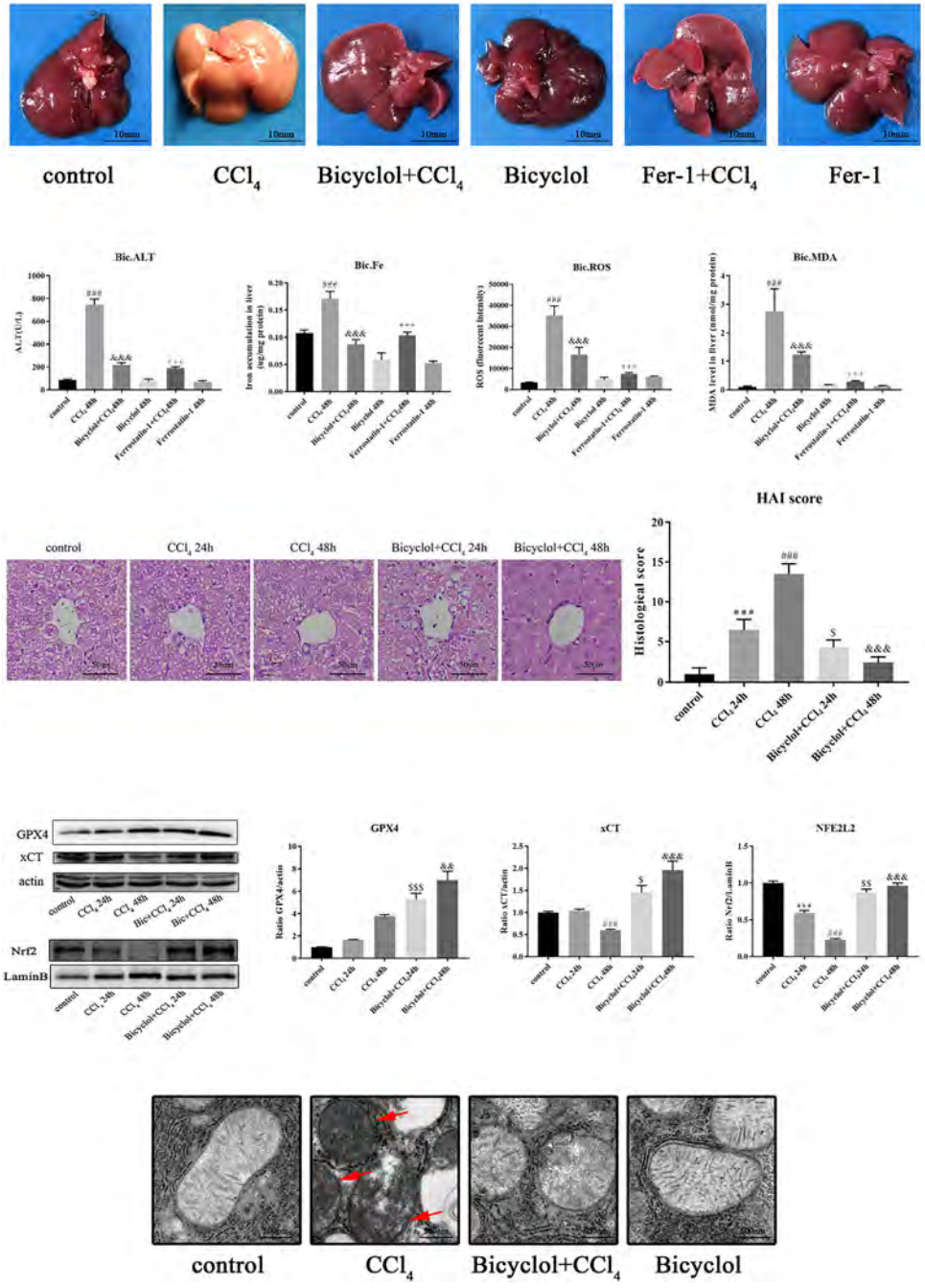
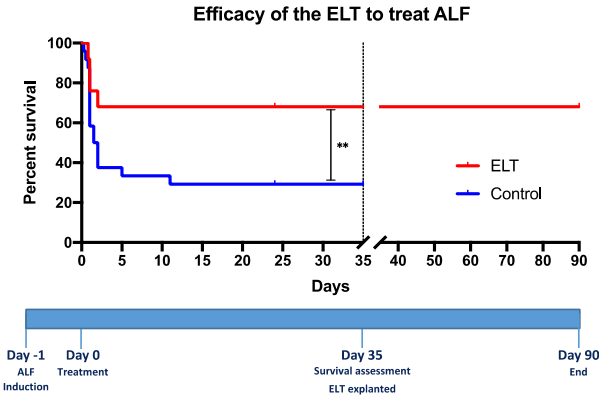


Figure: (abstract: AS027)

CCl4-induced fulminant liver failure, without immunosuppression, to assess survival in comparison to controls receiving the empty biomaterial (25 mice/group). We then assessed the biocompatibility, immunogenicity and tumorigenicity of our product both in vitro and in vivo.

Results: The human ELT effectively replaced liver functions and prevented death (68% survival at 5 weeks vs. 28% in controls, HR 0.3, $p < 0.01$) in immunocompetent mice with CCl_4-induced ALF, with no rejection or tumor formation (see Figure). Mice receiving the ELT showed less severe hepatic encephalopathy and an accelerated liver regeneration. The ELT was explanted from surviving mice at day 35, once their own liver had regenerated: all the animals survived long term with normal liver function. The immune-isolating capacity of the biomaterial was tested in vitro by mixed lymphocyte reaction: the biomaterial completely isolated embedded organoids (as well as activated dendritic cells used as positive control) from allogeneic T cells. Upon implantation into immunocompetent healthy mice, the human ELT did not trigger any inflammatory reaction, with no adhesions or foreign body reaction. At explant, after 4 weeks, the organoids within the ELT were alive and functional, without signs of rejection. No tumor or teratoma was observed after 16 weeks when encapsulated highly tumorigenic cells or undifferentiated iPSCs were transplanted into NSG mice, confirming the protective capacity of the biomaterial towards tumor formation.



Conclusion: Overall, we illustrate here the first stem cell-derived liver tissue capable of immediate, effective allogeneic replacement of liver functions in immunocompetent subjects with ALF, without the risk of rejection or tumor formation. The ELT has the potential of being developed into an off-the-shelf, allogeneic cell therapy to replace liver functions in patients with ALF without the need of immunosuppression.

AS029

Restricted protein intake in acute liver failure neither reduces ammonia nor improves cerebral edema but may increase risk of infection

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Background and Aims: Prevention or reversal of cerebral edema (CE) and hepatic encephalopathy (HE) is the cornerstone of management in acute liver failure (ALF). Since ammonia (NH_3) originates from breakdown of dietary proteins and hyperammonemia has been implicated in promoting CE; zero to low intake of dietary protein with slow increments in delivery is recommended. However, adequate protein is vital for preventing infection and maintaining eumetabolism. We studied the association of protein delivery with CE as measured by optic nerve sheath diameter (ONSD), arterial NH_3 levels and clinical outcomes in patients with ALF.
Method: In this prospective study, consecutive patients with ALF admitted to the Liver ICU (LICU) between December 2018 and September 2019 were enrolled. Information pertaining to clinical [HE status, requirement of continuous renal replacement therapy (CRRT), incidence of new-onset infections and ONSD] biochemical (arterial NH3) and nutritional (calorie and protein intake) parameters were recorded daily. Enteral nutrition (EN) was initiated within two hours of LICU admission using a standard EN formula. Individual EN provided 35–40 kcal and protein ranging from 0–2 g per kg ideal body weight (IBW) depending upon the clinical status and requirement for CRRT. The average protein intake of 7 days was categorized as low protein (LP: 0–1 gm/d) or high protein (HP: 1.1–2 g/d) and resolution of HE and incidence of new-onset infection was compared between LP and HP groups. The response of daily protein delivery (from baseline to day7) on ONSD and NH_3 was assessed using generalized linear model (GLM).
Results: In 40 patients with ALF [M-52%, age 32 ± 14.7 yrs; etiology-viral-30 (75%): DILLI-4 (10%): others-6 (15%); subtype-hyper acute-38 (95%): sub acute- 2 (5%); HE grade 2:3:4–2(5%): 4 (10%): 34 (85%); BMI- 25.54 ± 3.5 kg/m^2; ONSD- 4.6 (2.7–5.7); NH_3 -257 (89–839); lactate-4 (2–15)] enrolled, HE resolved in 15 (37.5%) and CRRT was done in 11 (27.5%). GLM assessment suggested no interaction of HP or LP with ONSD (beta = 1.095; p = 0.238) and NH_3 levels (beta = 198.11; p = 0.391). 24 (60%) patients received LP and 16 (40%) HP. There was no difference in the resolution of HE [LP 6(%) vs. HP 9(%); p = 0.738], though a trend to higher incidence of new infections was seen with LP diet [LP vs. HP = 10(25%) vs. 3(7.5%); p = 0.45].
Conclusion: Protein restriction practiced in patients with ALF admitted to an ICU is not helpful in preventing cerebral edema or lowering ammonia levels. However, zero or low protein intake may predispose the patients to an increased risk of infection.

AS030

Improved clinical and neurological outcomes in acetaminophen-induced acute liver failure: a twenty-one year, prospective multicenter study

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Background and Aims: Acetaminophen (APAP)-induced acute liver failure (ALF) is associated with significant mortality. Liver transplant (LT) in APAP-ALF presents challenges due to the rapidity and severity of illness, the potential for recovery without LT, and the presence of concomitant complex psychosocial issues. We aimed to evaluate trends in clinical interventions and important clinical outcomes over a 21-year period.
Method: We analyzed data from a multicentre retrospective cohort study of all APAP-ALF patients enrolled in the *United States ALF Study Group* prospective registry (1998–2018). Primary outcomes evaluated were 21-day transplant-free survival (TFS) and neurological complications. Covariates evaluated included enrollment cohort (early: 1998–2007, recent: 2008–2018), psychiatric comorbidity and the use of organ support including continuous renal replacement therapy (CRRT).

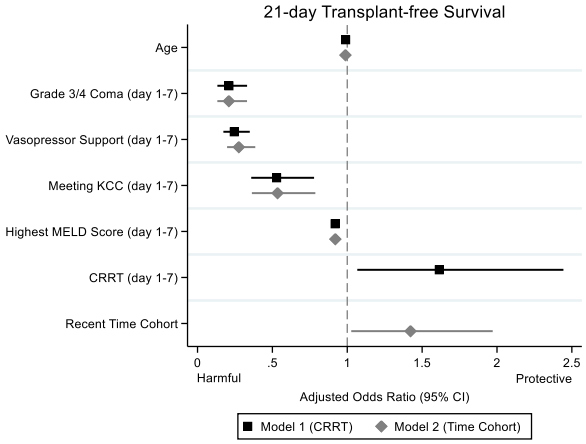

Figure: Independent associations with 21-day transplant free survival in 1190 APAP-ALF patients.

Results: There were 1190 APAP-ALF patients (early: n = 582; recent: n = 608). In comparing the recent and early cohorts, TFS was significantly lower in the recent (69.8 vs.61.7%, p = 0.005), with similar use of N-acetylcysteine. Recent cohort patients were more likely to receive CRRT (22.2% vs. 7.6), less likely to develop cerebral

edema (CE) (29.9% vs. 51.5%) or die to CE by day 21 (4.5%,vs. 11.6%; p < 0.001 for all). Stratifying by TFS status (non-TFS: n = 365 (273 died/100 transplanted) vs. TFS: n = 704), there were no differences in existing psychiatric comorbidity (51.5% vs. 55.0%; p = 0.3) or overdose intention (intentional: 39.7% vs. 41.6%; p = 0.6). During the first 7 days of study, TFS patients were less likely to develop grade 3/4 hepatic encephalopathy (HE; 52.7% vs. 91.5%), required less organ support (mechanical ventilation: 51.3% vs. 90.7%; vasopressors:19.5% vs. 65.8%; CRRT: 13.6% vs. 21.4%), and were less likely to develop cerebral edema by day 21 (CE; 22.1% vs. 61.4%; p < 0.002 for all). On multivariable logistic regression adjusting for vasopressor support (OR 0.25; 95% CI: 0.17–0.35; p < 0.001), development of grade 3/4 HE (OR 0.21; 0.13–0.33; p < 0.001), King's College Criteria (OR 0.53; 0.36–0.78; p = 0.001), and highest MELD score (per unit increase: OR 0.92; 0.90–0.94; p < 0.001), the use of CRRT (OR 1.61; 1.07–2.44; p = 0.02) was associated with TFS (c-statistic 0.86). In a second model substituting enrolment cohort for CRRT, recent enrolment was associated with improved TFS (OR 1.42; 95% CI: 1.03–1.97; p = 0.03; c-statistic 0.86).

Conclusion: Transplant-free survival in APAP ALF has improved over time while the incidence of CE/CE-related death has declined with improved intensive care support possibly related to increased CRRT use.

Cirrhosis – Experimental aspects

AS031

Toll-like receptor 4 inhibition acts synergistically with G-CSF to prevent organ injury and induce liver regeneration in acute-on-chronic liver failure

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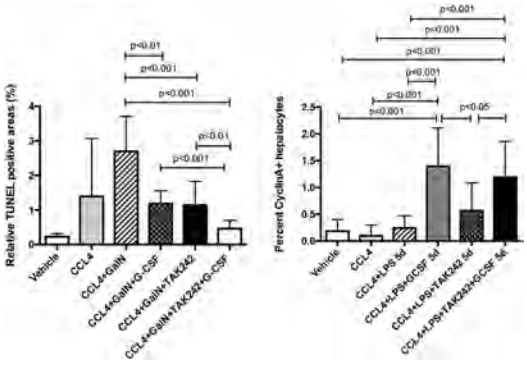
Background and Aims: Acute-on-chronic liver failure (ACLF) is characterised by lack of regeneration. Granulocyte colony stimulating factor (G-CSF) carries pro-regenerative properties and has been shown to be of benefit in ACLF. However, the large trial of G-CSF (GRAFT study) in patients with ACLF showed no benefit and in certain groups mortality tended to be higher. This study was performed to define the mechanisms underlying the negative effect of G-CSF and determine whether its beneficial effect could be harnessed using a toll-like receptor 4 (TLR4) antagonist.

Method: Two mouse models of ACLF were used: CCl4 (0.5 mg/ml,6w) to induce chronic liver injury followed by LPS i.p. (Klebsiella, 4 mg/kg) (n = 4–10) or Galactosamine (GalN) i.p. (1000 mg/kg) as a second hit (n = 8). 1 h after, G-CSF 250 μg/kg s.c. and/or TLR4-inhibitor TAK-242 10 mg/kg i.p. were injected and continued every 24 h. The treatment duration was 24 h and 5 d in the LPS model and 48 h in the GalN model. Samples were stored and analysed for liver injury, inflammation, senescence and regeneration.

Results: 6w CCl4 led to bridging fibrosis, TLR4 up-regulation and infiltration of G-CSFr expressing cells. LPS increased ALT levels, cell death (TUNEL+), enhanced hepatic infiltration of neutrophils (Ly6G+), macrophages (F4/80+) and TNFa. G-CSF increased the 48 h mortality from 0% to 66%, aggravated liver inflammation with macrophage and NK cell (CD45+,CD49b+,CD3-,CD19-) infiltration and IL6 expression. G-CSF+TAK-242 reduced the mortality to 0%, abrogated the liver injury (TUNEL) and liver inflammation (macrophages, neutrophils, TNFa, IL6) significantly. In the second model, GalN also induced a significant liver injury. Treatment with G-CSF+TAK-242 was significantly more effective than the individual therapies (figure). G-CSF +TAK-242 was associated with increased liver regeneration evidenced by increased tissue expression of pSTAT3 and BCL2. CCL4+LPS induced a p53 and p16-dependent cell cycle arrest and lack of proliferation (CyclinA) in hepatocytes. G-CSF+TAK-242 mitigated senescence and significantly increased the rate of CyclinA expressing hepatocytes (figure) suggesting enhanced liver regeneration.



Conclusion: The present study shows that G-CSF is deleterious in LPS-associated ACLF through further activation of inflammatory pathways and immune cell infiltration. TLR4 inhibition with TAK-242 prevented G-CSF driven tissue injury and induced liver regeneration showing evidence of synergy between the two molecules thereby providing a novel therapeutic strategy for ACLF patients.

AS032

A human liver cell-based system modeling a clinical prognostic liver signature combined with single cell RNA-seq for discovery of novel liver disease therapeutics

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Background and Aims: Chronic liver disease and hepatocellular carcinoma (HCC) are life-threatening diseases with limited treatment options. Previously, we have identified a pan-etiology 186-gene prognostic liver signature (PLS) in diseased liver tissues robustly predicting liver disease progression and HCC risk in patients with advanced liver disease (Hoshida *et al.*, N. Engl. J. Med. 2008; Nakagawa *et al.* Cancer Cell 2016). Efficient and high-throughput identification of candidate compounds for treatment of advanced liver disease and HCC has been hampered by the absence of tractable model systems.
Method: Here we developed a simple and robust human liver cell-based system modeling the clinical PLS of long-term liver disease progression and HCC risk for the major liver disease etiologies. Using the clinical PLS as a readout, we screened computationally enriched small molecules in the cell-based model (cPLS), followed by validation in NASH-HCC animal models and patient-derived tumor-spheroids. Using a recently developed single cell RNASeq pipeline (Aizarani et al. Nature 2019), we performed perturbation studies for mechanistic analyses.
Results: Our cPLS system robustly models the clinical PLS of long-term HCC risk within two weeks of cell culture, which takes two decades in patients. The clinical relevance of the cPLS was confirmed by similar transcriptomic dysregulation in the cell culture models and the diseased liver of clinical cohorts with corresponding liver disease etiologies. Using the cPLS model we identified a panel of previously undiscovered small molecules for treatment of advanced liver disease and HCC prevention. The two compounds scoring highest in reverting the poor-prognosis starts of the PLS were validated in two complementary NASH-HCC rodent models. Both compounds effectively inhibited liver fibrosis, inflammation and hepatocarcinogenesis *in vivo* confirming the validity of the approach. Using perturbation studies combined with single-cell RNA-Seq analyses of patient liver tissues, we unravelled previously undiscovered mechanistic roles of liver nonparenchymal cells in disease biology.
Conclusion: The cPLS model combined with single cell RNASeq analyses enables fast-track discovery of novel liver disease targets and therapeutics – a major global unmet medical need.

AS033

Neprilysin-neuropeptide Y axis as a target for treatment of liver fibrosis and portal hypertension

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Background and Aims: Chronic liver injury induces fibrosis and contraction of hepatic stellate cells (HSC) leading to fibrosis and portal hypertension (PHT). Importantly, the angiotensin converting enzyme (ACE) and angiotensin-II levels are involved in these processes. Neprilysin (NEP) is a neutral endopeptidase that cleaves neuropeptide Y (NPY), a 36 amino acid peptide described as a co-transmiter for contraction mediated by angiotensin II type 1 receptor (AT1R). Our aim is to study the effects of NPY and its cleavage mediated by NEP on fibrosis and PHT.
Method: Portal, hepatic, central and peripheral venous blood was collected from patients receiving transjugular intrahepatic portosystemic stent (TIPS) and analyzed for circulating levels of NPY. NEP expression was correlated with collagen1a1 expression in human fibrotic liver. *In silico* docking experiments reveals the effect of full-length NPY or the short NPY fragments cleaved by NEP on NPY type 1 receptor (Y1R). Liver fibrosis and PHT was induced in wild type (WT) and $Nep^{-/-}$ mice using bile duct ligation (BDL) (2 weeks) and carbon tetrachloride (CCl_4) (4 weeks) and hemodynamic changes were measured *in vivo*. Hepatic protein and mRNA expression were analyzed in these animals. *In vitro* analysis of primary HSC from WT and $Nep^{-/-}$ mice were incubated with NPY. In addition, fibrotic $Nep^{-/-}$ mice (BDL/CCl_4) were treated with AT1R blocker (losartan) or ACE inhibitor (captopril) for 2 weeks/4 weeks respectively.
Results: NPY levels increased in cirrhosis in humans and originates largely from portal vein. Hepatic NEP increases also with the severity of the disease but only in HSC. NEP deficiency in mice showed less fibrosis but higher hepatic NPY levels which induced PHT. *In vitro,* full-length NPY induces contraction of HSC by activation of Y1R but its fragments derived from NEP proteolysis, blocked Y1R and increased fibrosis in HSC. Molecular docking of NPY fragments to the receptor confirmed that NPY short peptides act as antagonist of the Y1R and act profibrotic. AT1R blockage (losartan) or ACE inhibition (captopril) in NEP deficiency mice, decreased fibrosis and portal pressure.
Conclusion: The link between fibrosis and contraction relay on the NEP/NPY axis. Dual NEP inhibition with AT1R blockade should be evaluated as a treatment to decrease fibrosis and portal hypertension in humans.

AS034

Endothelial portal venous damage is associated with alterations in local TM and EPCR expression in patients with cirrhosis and portal hypertension

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Background and Aims: Portal vein thrombosis is the most common thrombotic complication in cirrhosis, however its pathogenesis is still not fully understood. Endotoxemia, shear stress and inflammation secondary to portal hypertension, may lead to portal endothelial damage and disruption of its glycocalyx. Data regarding global haemocoagulative state in the portal vein are still scarce.
Method: We consecutively enrolled adult cirrhotic patients undergoing liver transplantation or transjugular-intrahepatic-portosystemic-shunt. Rotational-thrombelastometry (ROTEM), dosage of total circulating glycosaminoglycans (GAGs) and endotoxemia levels (LPS), along with evaluation of endothelial dysfunction by quantification of circulating endothelial-microparticles, were performed on citrated peripheral and portal venous blood samples of all enrolled patients.
Results: Forty-five cirrhotic patients were enrolled. ROTEM-analysis showed the presence of a heparin-like effect in portal blood by heparinase addition to the native test (median α angle NATEM® 50° vs HEPTEM® 55°, p = .027; median CT NATEM® 665 sec vs HEPTEM® 585 sec, p = .006), which was not detected in peripheral blood. This effect was consistent with the higher GAGs levels in the portal district compared to peripheral blood (median 4176 vs 2565 ng/ml, p < .001). The proportion MPs of endothelial origin, with respect to total Annessin V-MP, was significantly increased in the portal district (p = .036), highlighting a higher grade of endothelial damage in this site, which is in keeping with the higher concentrations of LPS (median portal 197 vs peripheral 165 pg/mL, p = <.001). Additionally, between endothelial MPs a decreased concentration in portal blood of those carrying thrombomodulin (median 232 vs 377MP/μL p = .002) and endothelial protein C receptor (median 16 vs 37MP/μL, p < 0.001), showed a specific impairment in the physiological anticoagulant properties of the endothelium of the portal vein.
Conclusion: In cirrhosis, portal vein is characterized by higher grade of endothelial dysfunction, glycocalyx damage and decerase in its anticoagulation function, associated with a higher concentration of LPS. These alterations may represent an important local risk factor in the pathogenesis of PVT.

AS035

The albumin-functionality-test (AFT) as a new valuable tool to assess human albumin function and predict ACLF in patients with decompensated cirrhosis

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Background and Aims: A major non-oncotic property of human albumin (HA) is the capacity of binding, transporting and detoxifying many endogenous and exogenous compounds. Structural HA damage occurs in patients with cirrhosis and, to a greater extent, in those with acute-on-chronic liver failure (ACLF), likely leading to functional impairment of the molecule. The Albumin-functionality-test (AFT) directly evaluates the ability of conformational mobility of HA, thus reflecting its residual binding function. This study aimed to assess the changes of AFT can discriminate patients with Acute Decompensation (AD) from those with ACLF and predict their prognosis.
Method: 319 patients with cirrhosis with acute decompensation (AD) were prospectively enrolled within 48 h from hospitalization. Serum samples were obtained at admission to measure the residual HA binding capacity by using the AFT based on electron paramagnetic resonance (EPR) spectroscopy to detect modified binding and functional characteristics of serum albumin. This is done by a comparison of three different mixtures of albumin, a spin labeled fatty acid and ethanol to simulate binding, transport and release conditions in vitro. Clinical and laboratory data were also collected and survival was recorded up to 1 year.
Results: AD alone was present at admission in 241 patients (76%) and ACLF in 78 (24%). Binding efficiency (BE) of AFT at admission was progressively reduced in patients with AD (38% [95%CI 36%–41%]) and to a more extent in those with ACLF (29% [95%CI 25%–32%]) as compared to the standard normal values. Moreover, AFT was inversely correlated with MELD (BE rho −0.346, p < 0.001; Detoxification efficiency (DTE) rho −0.342, p < 0.001) and Child-Pugh scores (BE rho −0.379, p < 0.001; DTE rho −0.362, p < 0.001).
32 patients (13%) developed ACLF within 30 days. Parameters derived from the AFT predict ACLF in patients with an AUC of 0.73 [95%CI 0.67–0.79] equal to that of the CLIF-C AD score (0.73 [95%CI 0.67–0.79]). However, when CLIF-C-AD score is combined with AFT parameters this significantly improves to an AUC of 0.83 [95%CI 0.78–0.88; p = 0.01]. AFT was also able to discriminate patients with a different probability of 1-year-survival: a binding efficiency higher than 35% at admission present a significantly higher survival rate than those with lower values (65% vs 48%, p = 0.001).
Conclusion: Based on these results, the AFT appears to be a promising tool to assess the residual binding function of the HA molecules in patients with decompensated cirrhosis, carrying also a potential role as a test for predicting ACLF and patient prognosis.

AS036

AXL-expressing homeostatic liver macrophages are reduced in patients with progression of cirrhosis

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Background and Aims: AXL and MERTK are phagocytic receptors with distinct patterns of expression. Their expression on circulating monocytes modulated innate immune responses in patients with advanced cirrhosis (CD14+HLA-DR+AXL+) and acute-on-chronic liver failure (ACLF, CD14+MERTK+) in relation to disease severity. AXL expression increased in response to PAMPs, phagocytosis and efferocytosis and involved enhanced efferocytosis, sustained phagocytosis and reduced TNF-α/IL-6 production and T cell activation, suggesting a homeostatic function. In tissues, AXL expression has been described on murine airway but not interstitial lung

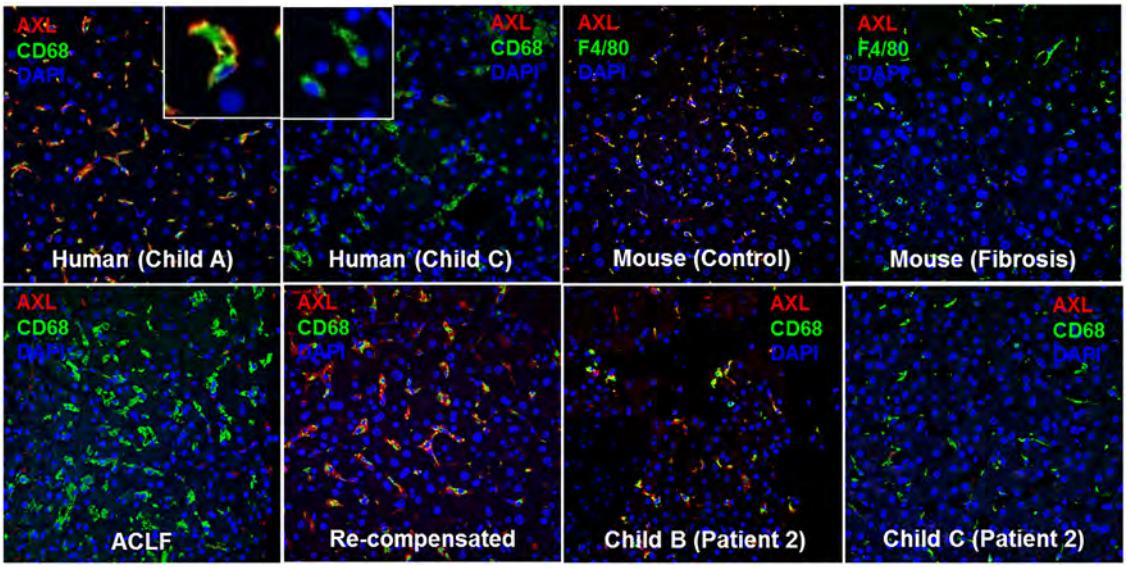

Figure: (abstract: AS036)

macrophages under homeostatic conditions, human Langerhans cells, and murine tissue-resident synovial lining macrophages. We sought to assess AXL expression in the liver of patients with cirrhosis.
Method: We used multiplexed immunofluorescence to compare AXL expression in liver biopsies from patients with cirrhosis (Child A n = 8; B n = 7; C n = 12) with healthy controls (HC n = 15), chronic liver disease (CLD n = 8), and nodular regenerative hyperplasia with portal hypertension (n = 3), and in a mouse model of CCl4 induced liver fibrosis (n = 5) and controls (n = 3). Longitudinal assessment of AXL expression was done in two patients: (1) with ACLF before and after re-compensation and (2) with progressive cirrhosis (from Child B to C). We evaluated AXL expression in gut biopsies from cirrhotic patients (Child A n = 7; B n = 5; C n = 4) compared to HC (n = 5) and ulcerative colitis (UC n = 5).
Results: AXL^+ cells were predominantly resident macrophages ($CD68^+$) but barely recently infiltrated macrophages ($MAC387^+$). Hepatocytes, stellate cells (SMA^+), and sinusoidal endothelial cells ($CD31^+CD34^+vWF^+$) did not express AXL. $CD68^+AXL^+$ cells significantly decreased with cirrhosis progression: (HC 90.2%; CLD 82.2%; Child A 76.1%; Child B 64.5%; Child C 18.7%; all $p < 0.05$). $CD68^+AXL^+$ cells in the liver of patients with non-cirrhotic portal hypertension were similarly reduced (59.4%). AXL^+CD68^+ cells negatively correlated with Child-Pugh ($p < 0.0001$), MELD score ($p = 0.0027$), and CRP ($p < 0.05$). AXL and MERTK were not co-expressed. AXL expression on macrophages from fibrotic mouse livers was lower compared to HC (21.7% vs. 95.4%, $p < 0.05$). Compared to HC, $CD68^+AXL^+$ cells were decreased also in gut biopsies from cirrhotic patients (HC 81.5%; Child A 65.6%, B 42.8%, C 36.6%; all $p < 0.05$).
Conclusion: We newly described AXL expression on the majority of resident macrophages in healthy liver which was reduced in advanced cirrhosis and portal hypertension. Loss of AXL expression was further observed on macrophages in gut tissue from cirrhosis patients. The data suggest a role for AXL expressing macrophages in hepatic immune homeostasis and barrier function of the liver and the gut.

Hepatitis C elimination

AS037

Community-based point-of-care hepatitis C testing and general practitioner initiated direct-acting antiviral therapy in Yangon, Myanmar (CT2 study)

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Background and Aims: The advent of direct-acting antivirals (DAAs) and near point-of-care testing for hepatitis C (HCV) facilitate improved community-based care. In many countries, access to DAAs is limited to tertiary hospitals but there is increasing recognition of the need for decentralizing care. This study demonstrates a decentralized hepatitis C care model in Myanmar.
Method: This study assessed the feasibility, acceptability and effectiveness of community-based POC testing and DAA therapy for HCV among people who inject drugs (Burnet Institute (BI) site) and general population (Myanmar Liver Foundation (MLF) site) in Yangon, Myanmar. Rapid diagnostic test (SD Bioline) for anti-HCV antibodies was performed on-site; if reactive, GeneXpert HCV RNA test was performed. External laboratory investigations for liver staging were undertaken for viremic patients. Results were given to the participant at next appointment with GP; participants commenced DAA therapy (sofosbuvir 400 mg/daclatasvir 60 mg) if specialist review was not required. Outcome data on HCV test positivity, treatment uptake and SVR12 rates as well as responses to behavioral surveys were collected.
Results: 633 participants were enrolled (n = 255 at BI; n = 378 at MLF). 256 (40%) reported lifetime injecting of drugs, of whom 236

(89%) had injected in the past six months. Other commonly reported risk factors included: family history (n = 87, 14%), surgery (n = 50, 8%), dental treatment (n = 32, 5%) and blood transfusion (n = 31, 5%). Of 633 enrolled, 606 (96%) were HCV antibody positive; of these, 606 (100%) received an RNA test. 537 (89%) were RNA positive and proceeded to pre-treatment assessments. Of these, 466 were eligible for DAA therapy on initial assessment, 22 required specialist review (all deemed eligible to start DAAs) and 488 (91%) were prescribed DAA therapy. Median number of days from RNA test to DAA prescription was 2 (IQR: 1, 5). To date, 244 have completed therapy and 126 are eligible for SVR12 assessment. Of those who have completed SVR12 assessment (n = 116 (92%)), 108 (93%) achieved SVR12.

Conclusion: The study results suggest providing community based POC testing and treatment initiated by general practitioners is feasible in low/middle income settings. Retention in care from diagnosis to treatment initiation and SVR12 rates were high among people who inject drugs and those with chronic liver disease. Evidence from this study will inform scale-up of hepatitis C treatment programs in Myanmar and globally.

AS038

Population-level hepatitis C cascade of care among men who have sex with men in British Columbia, Canada

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Background and Aims: Gay, bisexual and other men who have sex with men (MSM) are at higher risk of hepatitis C virus (HCV) acquisition. Although monitoring progress of MSM across the care cascade is critical to achieving HCV elimination goals, there is lack of data from the population based systems for monitoring progress among MSM. We constructed the cascade of care among people diagnosed with HCV infection living in British Columbia (BC), Canada in 2018, stratified by MSM status, to compare progress in care and treatment in this population.

Method: The BC Hepatitis Testers Cohort (BC-HTC) was used for this analysis. The BC-HTC includes all individuals tested for HCV in BC since 1990, with their data linked to all prescription drugs, medical visits, hospitalizations and mortality data. We defined six cascade of care stages: 1) anti-HCV positive (diagnosed); 2) RNA tested; 3) RNA positive, 4) genotyped; 5) initiated treatment; and 6) achieved a post-treatment sustained virologic response (SVR). We compared progression through the care cascade by MSM status. MSM identification was based on self-report as well as validated algorithm which imputed missing information with 95% specificity.

Results: Of 33,647 males diagnosed with HCV and alive in 2018, 3,940 were MSM and 29,707 were non-MSM. Slightly more MSM (3,314, 84%) received confirmatory HCV RNA testing compared non-MSM (24,264, 82%). Among those with a positive RNA test, there was no difference in progression to genotyping between the MSM and non-MSM groups (2,231, 90% vs 16,514, 90%). However, slightly more MSM initiated treatment than non-MSM (1,406, 63% vs 9,964, 60%). There was a substantial increase in treatment uptake between 2012 and 2018 among both groups (MSM: 37% to 63%; Non-MSM: 36% to 60%). Among those who were RNA positive, treatment uptake was slightly higher among MSM than non-MSM (1,406/ 2,473, 57% vs. 9,964/ 18,427, 54%). Among those who received treatment and were assessed for SVR, a similar proportion achieved SVR (MSM: 1,011/ 1,111, 91% vs non-MSM: 6,608/7,319, 90%).

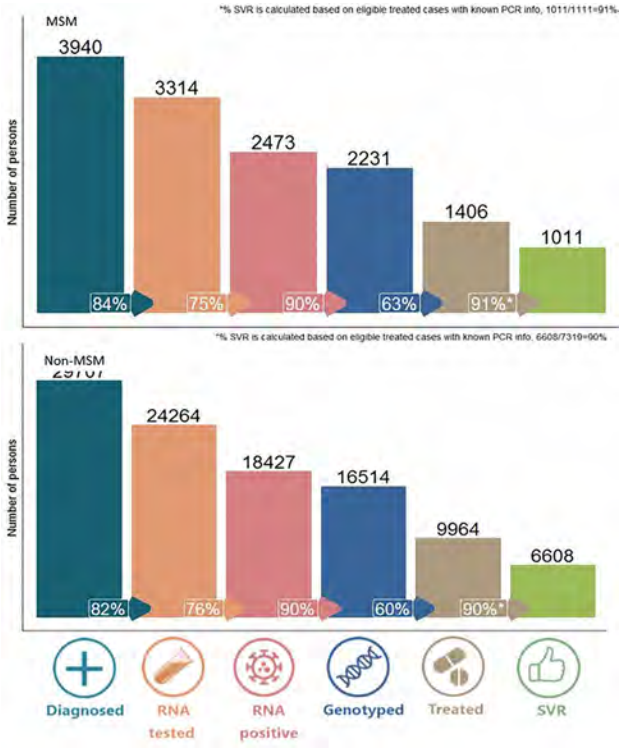

Figure: HCV care cascade among MSM and non- MSM groups in British Columbia in 2018

Conclusion: There has been substantial progression across the care cascade stages after introduction of DAAs. MSM had slightly better progression than non-MSM across the testing, care and treatment cascade.

AS039

Decline in HCV incidence in HIV positive MSM - progress to HCV micro-elimination in the UK?

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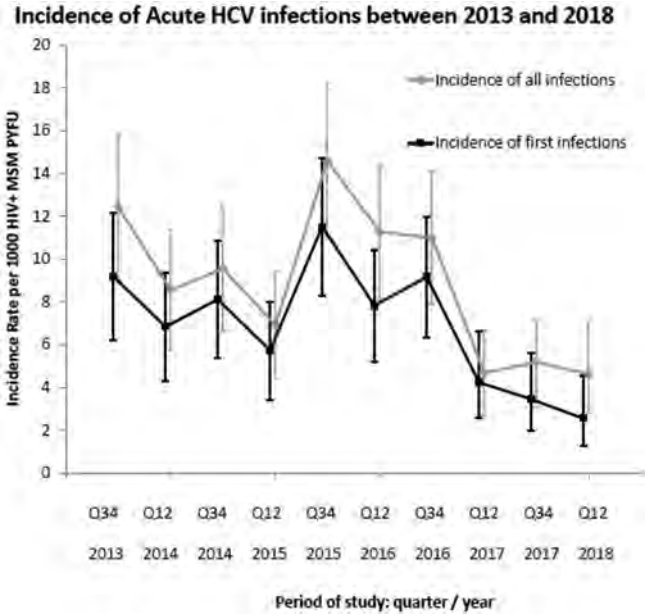
Background and Aims: Modelling of the London hepatitis C (HCV) epidemic in HIV-positive (HIV+) men who have sex with men (MSM) suggested early access to direct acting antiviral (DAA) treatment may reduce incidence. With high rates of linkage to care, micro-elimination of HCV within HIV+ MSM may be realistic, ahead of 2030 WHO targets. We examine trends in HCV incidence in the pre- and post-DAA eras for HIV+ MSM in London and Brighton.

Method: A retrospective cohort study was conducted at 5 HIV clinics in London and Brighton between 2013 and 2018. Each site reported all acute HCV episodes (first and reinfections) during the study period. Treatment pathway and timing were collected. Incidence rates and reinfection proportion were calculated.

Results: 378 acute HCV infections were identified, comprising 292 first infections and 86 reinfections. Incidence rates of acute HCV in HIV+ MSM peaked at 14.57/1000 PYFU [95%CI 10.95–18.20] in the second half of 2015. Rates fell to 4.63/1000 HIV+ MSM PYFU [95%CI 2.60–6.67] by 2018. Proportion of reinfections increased to 45% by 2018. Time from diagnosis to starting treatment reduced from 29.8 (2013) to 3.7 months (2018).



Conclusion: We observed a 78% reduction in incidence of first HCV episode and 68% reduction of overall HCV incidence in HIV+ MSM since the epidemic peak of 2015 which coincides with wider access to DAAs in England. However reinfection may be increasing. Further interventions to reduce transmission, including earlier access to treatment and for reinfection, are likely needed for micro-elimination to be achieved in this population.

AS040

Hepatitis C infection in the Spanish prison system. Elimination is a dream at our fingertips

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Background and Aims: Spanish Program to tackle hepatitis C infection included the prison setting as priority to treat all inmates regardless fibrosis stage from the early beginning of the plan. Actually, HCV treatment is extended to almost all the prisons, thus it is speeding up the goal of elimination. Many microelimination programs are ongoing, however we lack global data regarding HCV management within the Spanish Prison System. We aim to describe hepatitis C situation in Prison across the Spanish Country.
Method: We analyzed the systematic registry of the informatic database of Health Penitentiary Coordination Department of Spain, including registries from January 2015 to June 2019. This involved 71 prisons, and it did not include those in Catalonia.
Results: We found: 49,976 inmates in 2015, 49,224 in 2016; 47,803 in 2017; 47,901 in 2018 and 47,499 in 2019. Mean turnover rate was 58% (±47). Screening rate was 60.9% in 2015, 66.5% (2016), 48% (2017), 79% (2018) and 79% in 2019 ($p < 0,001$). This rate was lower in centers with higher turnover rate. Viremia prevalence is greatly decreasing across these years: 11% – 2016; 9% – 2017; 3% – 2018 and 1.9% – 2019. Regarding HCV genotype, globally we found 1a (31%), then 3 (18%) and 4 (12%); 1b (8%) and 1 (3%); 28% was undetermined. Overall, advance fibrosis (F3-F4) was found in 34%, however it has decreased from 57% in 2015 to 25% in 2019. SVR rates were independent of viral load, genotype, fibrosis stage and prison features. The decrease in prevalence has been independent of the region, the type of the prison, the number of inmates or the turnover rate. We observed a reduction in the incidence, going down from 0,47 in 2010 to 0,29 (per 1000 inmates/year) in 2018 ($p < 0.01$). Mean global mortality in the penitentiary setting is 0.28% in the last years. HCV-related mortality has come down from 0.018 in 2015 to 0.002 in 2018.
Conclusion: The emergence of direct acting antiviral for HCV and its universal access in the penitentiary setting has led to a significant decrease in the prevalence of HCV infection. The prison system provides high screening and treatment rates that are close to WHO recommendations to achieve elimination in this group.

AS041

Evaluating and communicating hepatitis C cascades of care data: a journey towards elimination in Tayside, Scotland

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Background and Aims: Chronic Hepatitis C Virus (HCV) is one of the leading causes of liver cirrhosis and hepatocellular carcinoma, presenting a significant burden to global health systems, but is curable. The WHO 2030 Elimination Goals need each country to evaluate their response to their epidemics. This can be achieved by visualisation of Cascades of Care, depicting how infected cases move through disease stages. However, current methods of displaying HCV data are debated and lack practical application. This project proposes a fresh way of codifying and displaying HCV data using Tayside, Scotland as a case study.
Method: 1164 cases of active HCV infections in those that were alive and resident in Tayside between January 2015 and December 2018 were analysed from NHS Tayside's HCV Database. All those diagnosed, treated, and cured before 2015 were removed from the prevalence. Variables were evaluated to create a systematic coding framework that was then used to code each patient's diagnosis, treatment, and cure status each year from 2015–2018.
Results: Graphical representation of the data in the form of stacked clustered bar charts and cumulative line graphs demonstrate general trends and conversion rates: Tayside has seen a steady new HCV diagnosis rate and increase in treatment and cures, leading to a 3-fold increase in diagnosis-to-cure conversion rates from 15.36% (2015) to 43.77% (2018). This graphical representation also demonstrates how effectively previously diagnosed people and newly diagnosed people are accessing treatment: on average 24.94% of previously diagnosed and 34.31% of newly diagnosed patients are successfully engaging in treatment each year in Tayside. Cumulative data graphs show clear progress towards goals: Tayside shows encouraging progress towards WHO elimination targets with 77.9% of prevalent cases since 2015 were diagnosed, 71.0% treated, and 66.6% cured.
Conclusion: This project proposes a novel way of displaying Cascades of Care data that relays yearly snapshots of an epidemic, cumulative progression over time, nuanced information of each stage, and progression towards elimination targets. This method can be used in a meaningful way to improve local service planning, knowledge

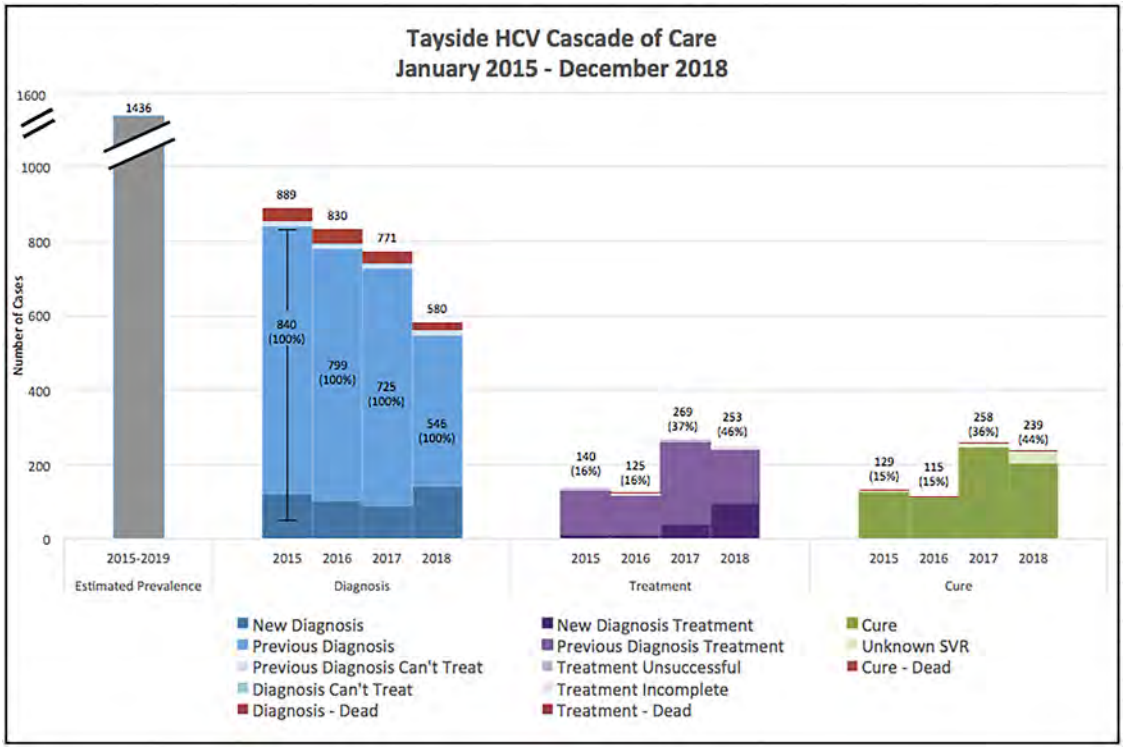

Figure: (abstract: AS041)

exchange across health systems globally, and reporting to bodies like the WHO.

AS042

Progress towards achieving hepatitis C elimination in the country of Georgia, April 2015-October 2019

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Background and Aims: In April 2015 with the technical assistance of U.S. CDC and commitment from Gilead Sciences to donate direct acting antivirals (DAAs), Georgia launched the world's first HCV elimination program. A key strategy of the program is nationwide HCV screening, active case finding, linkage to care, provision of treatment for all HCV-infected persons and effective prevention interventions. The elimination program aims at achieving 90–95–95 targets by 2020: a) diagnose 90% of HCV-infected persons, b) treat 95% of those diagnosed, and c) cure 95% of those treated. We report progress towards elimination targets 4 years into the elimination program.

Method: A hepatitis C care cascade was constructed using data from the national HCV treatment program (Figure). A national serosurvey in 2015 estimated that 150,000 over 18 years of age were infected with HCV in the country. The program collects data on all persons registered with the treatment program. Treatment was provided with Sofosbuvir, Ledipasvir/Sofosbuvir or Velpatasvir/Sofosbuvir-based regimens. Data on persons tested for chronic HCV infection through sustained virologic response (SVR) were extracted as of October 31, 2019.

Results: Overall 121,043 persons tested positive for HCV antibodies and of those 97,348 (80.4%) underwent HCV confirmatory testing. Chronic HCV infection was confirmed in 79,955 (82.1%) persons, representing 53.3% of the estimated 150,000 adults living with HCV. A total of 62,927 (78.7%) patients initiated treatment – 49.1% of the estimated target population to be treated (128,250). Of the 41,220 patients who were evaluated for SVR, 40,693 (98.7%) tested negative for HCV by PCR, representing 33.4% of the estimated target population to be cured (121,837). Very high cure rates were achieved for all HCV genotypes: 98.9% in genotype 1, 98.9% in genotype 2 and 98.3% in most challenging to treat genotype 3. Treatment effectiveness was comparable among persons with advanced fibrosis (F3 and F4) with 98.2% achieving SVR, and among patients with mild or no liver fibrosis (≤F2), SVR = 99.0%.

Conclusion: Georgia has made substantial progress towards eliminating hepatitis C, with more than half of persons with HCV infection identified and registered for treatment. Very high cure rates have been achieved among those who received SVR testing. Challenges remain in identifying and especially linking to care persons living with HCV in Georgia. Nationwide integrated, decentralized model of HCV treatment, which is already implemented, will be critical to improve linkage to care and close the gaps in HCV cascade.

Complications of cirrhosis and ACLF

AS043

Adherence to surviving sepsis campaign 3-hour bundles improves survival in non-critically ill patients with cirrhosis and sepsis

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Background and Aims: Sepsis is a common and life-threatening complication in cirrhosis. Surviving Sepsis Campaign recommendations suggest treatment bundles for sepsis. The early administration of sepsis bundles reduces mortality in general population, however no data is currently available in patients with cirrhosis. The aim of this study was to evaluate whether the adherence to 3-hour bundles could modify clinical outcomes in patients with cirrhosis and sepsis.
Method: From January 2012 to May 2019 consecutive non critically-ill patients with cirrhosis and bacterial infections were enrolled. Clinical, laboratory, microbiological and treatment data were collected at the diagnosis of infection and during the whole hospitalization. Adherence to 3-hour bundles (namely microbiological cultures obtained before the administration of antibiotics, administration of broad spectrum antibiotics within 3 hours and assessment of blood lactates) was assessed. Patients with sepsis were identified according to Sepsis-3 criteria recently adapted to patients with cirrhosis. Patients were followed up until death, liver transplantation (LT) or up to 90 days. LT was considered a competing event for death in survival analysis.
Results: 144 out of 329 patients with cirrhosis and infections had sepsis and were included in the analysis. (Age = 62 ± 11 years; MELD score = 23 ± 7). The most common infections were SBP (24%), pneumonia (22%) and spontaneous bacteremia (19%). Microbiologic cultures were obtained before antimicrobial therapy in 98 (68%) patients, broad spectrum antibiotics were given within 3 hours in 79 (55%) patients while lactates were measured in 69 (48%) patients. The adherence to the full 3-hour bundle was achieved in 27 (19%) patients.

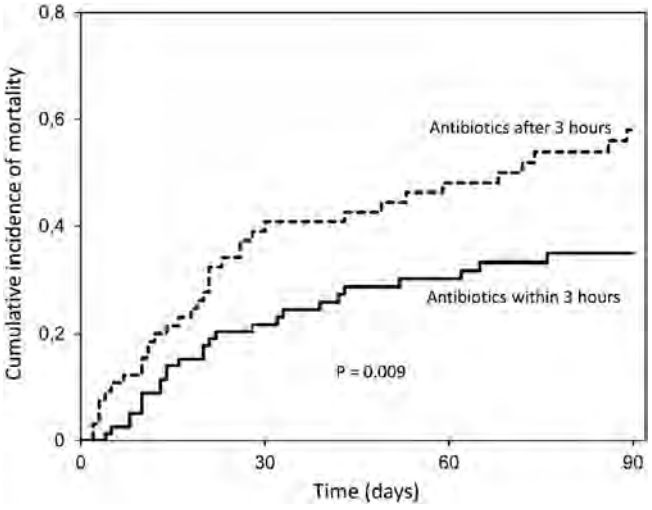

Figure: Cumulative incidence of mortality according to timing of antibiotic treatment.

The administration of empiric broad-spectrum antibiotics within 3 hours was associated with lower 28-day (22% vs 39%; p = 0.024) and 90-day cumulative incidence of mortality (35 vs 58%; p = 0.009; Figure). Mortality was further reduced in patients receiving antibiotics within 1 hour.
In multivariate competing risks analysis (adjusted for age, MELD score, ascites and hepatic encephalopathy) both adherence to the 3-hour antibiotic bundle (sHR = 0.46; p = 0.019) and culture bundle (sHR = 0.47;p = 0.027) were independently associated with better 28-day survival, while the measurement of lactates did not influence 28-day survival (sHR = 0.85; p = 0.63).
Conclusion: The adherence to the 3-hour antibiotic and culture bundles was associated with lower mortality in patients with cirrhosis and sepsis. However, the adherence to these bundles was not optimal and strategies should be developed to improve the adherence to sepsis bundles in patients with cirrhosis.

AS044

Stage 1b acute kidney injury in cirrhosis is likely due to underlying chronic kidney disease and would be more appropriately re-classified as acute-on-chronic kidney disease

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Background: Stage 1 acute kidney injury (AKI) in cirrhosis (rise in serum creatinine [sCr] by ≥ 0.3 mg/dL in <48 hrs, or by 1.5 to 2.0 times from baseline) has been subdivided by EASL into stages 1a & 1b, with the final sCr being < or ≥ 1.5 mg/dL respectively, with stage 1a patients having a benign course but not stage 1b patients. However, stage 1b AKI diagnosis requires a relatively high baseline sCr (between 1.0 mg/dL for 50% increase of sCr, to 1.2 mg/dL for a Δ of 0.3 mg/dL), suggesting that there may be background chronic kidney disease (CKD). **Aim:** To test the hypothesis that a high baseline sCr is the basis of stage 1b AKI development, and is associated with a worse prognosis than stage 1a AKI.
Method: Admitted ascitic cirrhotic patients who developed stage 1 AKI per the International Ascites Club 2015 definition from the NACSELD database were included, comparing patients with stage 1a vs. 1b AKI with respect to demographics, laboratory values, AKI treatment response and survival.
Results: 419 of 2297 enrolled patients developed stage 1 AKI (1a: 43%). Stage 1b patients were older (60 ± 10 vs. 57 ± 10 years, p = 0.04), more had refractory ascites (60% vs. 39%, p < 0.0001), and more were on rifaximin (51% vs. 39%, p = 0.014). Otherwise, both subgroups had similar demographics, prevalence of diabetes, 6-month history of hospital admissions, and medication use. Significant differences were noted in their baseline renal function, MELD scores and response to treatment (Table). Significantly more stage 1b patients were treated for their AKI with midodrine (30% vs. 13%, p < 0.0001), with more

albumin being infused (289 ± 218 gm vs. 229 ± 245 gm, p = 0.005). More stage 1b patients needed RRT initiation (10% vs. 1%; p = 0.0001), with worse survival (Table).

	Stage 1a (n = 180)	Stage 1b (n = 239)	P value
Baseline sCr (mg/dL)	1.02 ± 0.30	2.02 ± 1.17	<0.0001
Baseline eGFR (ml/min)	66 ± 27	31 ± 12	<0.0001
Admission sCr (mg/dL)	1.16 ± 0.23	2.47 ± 1.34	<0.0001
Peak sCr (mg/dL)	1.49 ± 0.40	2.79 ± 1.52	<0.0001
Δ sCr (mg/dL)	0.48 ± 0.26	0.78 ± 0.66	<0.0001
Admission MELD	18.33 ± 6.27	24.58 ± 7.32	<0.0001
Course of AKI:			<0.0001
Transient	74% (125/168)	54% (126/232)	
Persistent	22% (37/168)	28% (66/232)	
Progressive	4% (6/168)	17% (40/232)	
30 day transplant free survival	88% (158/180)	77% (183/239)	0.0035

Conclusion: The worse prognosis in Stage 1b AKI patients is related to a more progressive AKI course, likely due to the presence of underlying CKD in the majority. Therefore, stage 1b AKI in cirrhosis should be assessed separately for natural history and treatment strategies.

AS045

Prophylaxis with norfloxacin is not associated with multi-drug resistant bacterial infections

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Background and Aims: The role of norfloxacin in the development of bacterial infections by multi-drug resistant organisms (MDRO) is controversial. We evaluated the effect of prophylaxis with norfloxacin in the development of MDRO infections in patients with cirrhosis.

Methods: Multicenter prospective cohort study (clinicatrials.gov NCT03919032) of cirrhotic patients with bacterial infections throughout Argentina. The outcome variable was infection caused by MDRO (culture-negative infections were classified as non-MDRO). The main exposure of interest was norfloxacin prophylaxis at the time of the bacterial infection (patients with other prophylaxis were excluded). We evaluated the effect of norfloxacin on MDRO using a weighted logistic regression model for the inverse of the probability of treatment. We used stabilized weights generated through a logistic regression model considering age, gender, cirrhosis etiology, MELD, medications (beta-blockers, proton pump inhibitors, immunosupressors and rifaximin); recent invasive procedures, therapeutic antibiotic use and hospitalizations; history of ascites, bacterial infections and infection/colonization by MDRO; diabetes; and whether patients were treated in a transplant center or not.

Results: A total of 383 patients from 20 centers were included, 46 (12%) were on prophylaxis with norfloxacin. The most frequent infections were SBP (29%) and urinary tract infection (24%). MDRO were isolated in 85 (22%) patients: 11 (24%) with norfloxacin prophylaxis and 74 (22%) without norfloxacin prophylaxis (p = 0.765). The most frequent MDRO were enterobacteriaceae (63%) and methicillin-resistant staphylococcus aureus (15%). Patients with norfloxacin had higher MELD and were more likely to have received rifaximin and proton pump inhibitors and to have a history of invasive procedures than patients without norfloxacin (Table). No association was found between norfloxacin use and infection by MDRO in the weighted analyses considering the variables detailed in methods (OR_{IPW} 2.84, 95% CI, 0.66 to 12.32; p = 0.162).

	Without norfloxacin (n = 337)	With norfloxacin (n = 46)	p
Age – years*	59 (51–66)	50 (60–64)	0.810
Male**	220 (65.3)	34 (74.0)	0.751
MELD*	17 (13–23)	20 (16–27)	0.012
Diabetes**	107 (31.9)	15 (32.6)	0.927
Rifaximin**	84 (25.1)	24 (52.2)	<0.001
Proton pump inhibitor**	123 (37.2)	29 (63.0)	<0.001
Recent antibiotic treatment**	107 (32.8)	20 (43.5)	0.156
Recent invasive procedures**	113 (35.3)	26 (59.2)	0.003
Prior isolation of MDRO**	15 (4.7)	3 (6.7)	0.571
Nosocomial/HCA infection**	153 (45.3)	30 (65.2)	0.053
Ascites**	251 (74.5)	40 (86.9)	0.070
Prior bacterial infections**	63 (20.0)	15 (35.0)	0.025

*Median (IQR); **Number (%).

Conclusion: The results of our study, which applies methods that strengthen causal inference, reinforces that prophylaxis with norfloxacin is not associated with infections by MDRO.

AS046

Risk of mortality in patients with uncontrolled variceal bleeding is determined by the presence and severity of acute on chronic liver failure (ACLF) and early transjugular intrahepatic portosystemic shunt (TIPSS) reduces long term mortality

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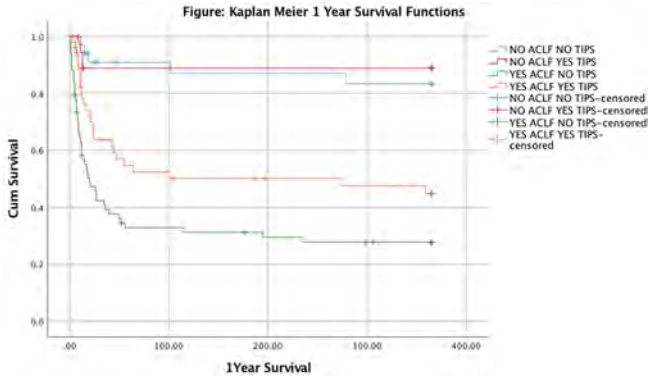
Background and Aims: Mortality of patients with variceal bleeding (OGVB) that is uncontrolled with endoscopic therapy is associated with a high-risk of mortality. ACLF occurs in cirrhotics and is

characterized by organ failure(s) and high-risk of mortality but whether it is of prognostic significance in OGVB patients is not known. Early TIPSS insertion in patients with ongoing bleeding is thought to improve survival, but whether patients with ACLF will benefit is not clear. The aims of this study were to determine whether ACLF and its severity defines the risk of death and whether TIPSS improves the survival of patients with poorly controlled OGVB and ACLF.

Method: From a prospectively maintained registry kept by the ICU, Royal Free Hospital (RFH), data of 174 consecutive patients with OGVB and evidence of ongoing bleeding despite endoscopic therapy between 2005 and 2015, who were admitted to ICU were included. All patients were managed according to the standard of care for acute OGVB and organ support was instituted when required. Early TIPSS was defined as technically successful TIPSS done within 72 hours of an acute OGVB episode. Standard statistical tests were used to address the above questions and Cox regression was used for multivariate modelling.

Results: ACLF patients (n = 120) were significantly different to AD (n = 54) [older age: p = 0.03; ascites: p = 0.002; hepatic encephalopathy: p < 0.001; >organ failures (p < 0.001); >white cell count (p = 0.007); >INR (p < 0.001); >bilirubin and creatinine (p < 0.001)] but the number of bleeds and transfusion requirements were similar. 28-day, 90-day and 1-year mortality in the AD patients was 9.3%, 9.3% and 13% compared with 46.7%, 55.8% and 60.8% in the ACLF groups (p < 0.001) respectively (Fig); mortality increased with increasing ACLF grade (p < 0.001). TIPSS was inserted in 72 patients [(Median time to TIPSS from Index bleed 1 day, (IQR: 0–3)] (AD: 20 (37%); ACLF: 52 (43%) (p = 0.4), which reduced mortality of ACLF (p = 0.01) but not in AD patients. In the multivariable model in patients who had ACLF, age (p = 0.009), temperature (p = 0.022), white cell count (p = 0.029), CLIF-OF score (1.323(1.111–1.576); p = 0.002) and TIPS placement (0.546(0.302–0.987); p = 0.045) (Fig) were independent predictors of mortality.



Conclusion: This study shows for the first time that, OGVB that is not controlled with endoscopic therapy, the presence and severity of ACLF and systemic inflammation determines the risk of 28-day and 1-year mortality. Early TIPSS improves the survival of ACLF patients.

AS047

Increased survival in patients with hepatic encephalopathy treated with rifaximin-alpha in combination with lactulose: an observational study from UK clinical practice

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Background and Aims: Hepatic encephalopathy (HE) is a neuropsychiatric complication of cirrhosis signalling hepatic decompensation. Overt HE episodes are medical emergencies that render patients' incapable of self-care, and frequently result in hospitalisation, coma, and/or death. In randomized studies, rifaximin-alpha (RFX) in combination with lactulose (LCT) significantly reduced the risk of HE episodes and overt HE-related hospitalisations compared with LCT alone. It has been postulated that treatment with RFX should increase life expectancy in these patients. In this study, our aim was to evaluate the impact of RFX treatment on survival in "real-world" patients with HE in the United Kingdom (UK).

Method: Anonymised primary and secondary care health records from the Clinical Practice Research Datalink (CPRD) sourced HE patients treated with RFX and LCT, either as monotherapy or in combination, from 2003 to 2019 in primary care. Treatment was assumed to last for 28 days either side of prescription date. The primary endpoint was all-cause mortality (ACM) confirmed by national registration. Time to event from first proxy HE diagnosis (index) was analysed by extended Cox proportional hazards regression, where treatment and other covariates were modelled as monthly, updated, time-dependent parameters to maximise data availability.

Results: There were 4,669 patients newly diagnosed with HE, of which 61% were male, with a mean age of 59 years (SD 13), for whom 1,107 years of RFX, 1,500 years of LCT, and 1,157 years of RFX+LCT treatment were recorded. In total, 2,039 deaths were observed, at a rate of 271 per 1,000 person years. Compared to LCT-alone, RFX+LCT had an adjusted hazard ratio for ACM of 0.82 (95%CI: 0.70 to 0.96), while for RFX-treatment the aHR was 1.11 (95%CI: 0.94 to 1.30). Other ACM co-variables included age, gender, prior liver cancer, ascites, platelet count, estimated glomerular filtration rate, albumin and sodium.

Conclusion: Treatment with RFX+LCT improved survival compared to LCT-alone in routine clinical practice in the UK.

AS048

Supplementation with branched-chain amino acids improves muscle mass of cirrhotic patients with sarcopenia

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Background and Aims: It is controversial whether sarcopenia can be reversed in patients with liver cirrhosis. On the other hand, the effect of branched-chain amino acids(BCAA) supplementation on protein

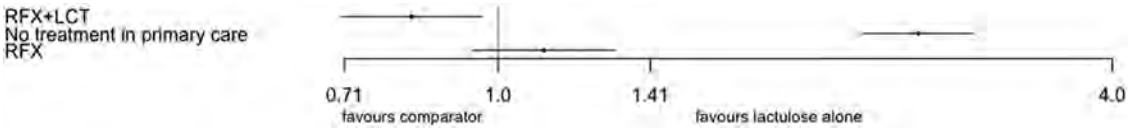

Figure: (abstract: AS047): Forest plot for RFX+LCT, RFX, and no treatment in primary care versus lactulose.

and albumin synthesis is known. However, the role of BCAA on skeletal muscle mass in patients with cirrhosis and sarcopenia is unknown.
Method: Pilot, prospective, randomized and double-blind study of a cohort of patients with cirrhosis and sarcopenia diagnosed by CT scan. Each envelope of BCAA contained: 15 g of protein, 8.5 g of fat, 68 g of carbohydrates, BCAA(leucine, isoleucine and valine), additional vitamins and minerals. The study protocol was approved by the Institutional Review Boards(PI11.17) and was registered at ClinicalTrials.gov(NCT04073693).
Results: 32 patients performed nutritional and physical activity intervention for 12 weeks. Divided into2groups: 17patients in placebo group and 15patients in BCAA group. Baseline characteristics were similar in both groups. No adverse effects or hepatic decompensation were reported during the intervention. All patients maintained good adherence to nutritional supplements and increased a median of 2000steps(1000; 2500) in both groups($p = 0.22$). At 12 weeks after the start of treatment, BCAA group had a higher increase in zinc levels than placebo group(Δzinc:12.3 vs. 5.5;$p = 0.026$). In addition, there was a tendency for higher improvement of albumin in the BCAA group(Δalbumin:0.19 vs. 0.04;$p = 0.091$). After treatment, only BCAA group presented a significant improvement in muscle mass(Δmuscle mass: 2.3 vs. 0.04; $p = 0.022$). Muscle mass after treatment with BCAA was significantly higher than baseline (43.7 vs. 46 cm^2/m^2; $p = 0.023$). This difference between post and pre-muscle mass was not evident in the placebo group (44.5 vs. 44.6 cm^2/m^2; $p = 0.936$). 5 patients (18.5%) presented resolution of sarcopenia. Although this resolution was more prevalent in the BCAA group, the difference was not statistically significant (25 vs. 13.3%; $p = 0.628$). Likewise, there was improvement in muscle mass in 17 patients(63%). Muscle mass improvement was more frequent in the BCAA group (83.3 vs. 46.7%; $p = 0.056$). Regarding the evaluation of frailty after 12 weeks of intervention, there were no differences between groups(ΔLiver Frailty index: −0.37 vs. −0.31; $p = 0.581$). However, in the global cohort of patients ($n = 32$), there was a significant improvement in the Liver Frailty index after 12 weeks of intervention (4.2 vs. 3.9; $p < 0.001$). This difference was significant in both groups, both in the placebo group (4.2 vs. 3.8; $p < 0.001$) and in the BCAA group (4.2 vs. 3.9; $p < 0.001$). Regarding liver function, there were no differences in the modification of MELD score during the follow-up (ΔMELD: 0.6 vs. 0.3; $p = 0.695$).
Conclusion: BCAA supplementation for 12 weeks improves muscle mass measured by CT scan in patients with cirrhosis and sarcopenia.

Immunity and Hepatocellular Carcinoma

AS049
Identification of a panel of safe immunogenic antigens for therapeutic vaccination strategies in hepatocellular carcinoma

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Background and Aims: Cancer/testis antigens (CTAs) are frequently overexpressed in tumor cells and most lack expression in healthy adult tissues, excluding the immune-privileged testis. This, combined with being immunogenic, makes CTAs attractive targets for therapeutic vaccination in cancer patients. We aimed to define a panel of immunogenic testis-restricted CTAs, of which each CTA is expressed in ≥ 10% of hepatocellular carcinoma (HCC) tumors, that can be used for off-the-shelf vaccination-strategies in HCC.
Method: Literature and database study identified 50 CTAs supposedly expressed in HCC and not in healthy tissues. mRNA expression of CTAs was determined by RT-qPCR in healthy livers ($n = 21$), healthy adult tissues ($n = 22$ different tissues), and paired tumor and tumor-free liver (TFL) tissues ($n = 100$; obtained after resection with curative intent). Immunogenicity was established by measuring proliferation of peripheral blood T-cells from 14 HCC patients (treated with local ablative therapy) against autologous B-cell blasts transfected with CTA-encoding mRNA.
Results: Of the 50 selected CTAs, 24 were excluded due to mRNA expression in healthy livers. Of the remaining 26 CTAs, 12 were expressed in tumors of ≥ 10% of HCC patients and not in any healthy tissue except testis. Seventy-nine percent of HCC patients expressed at least one of these CTAs and >50% of patients expressed at least 3. Interestingly, in 45% of HCC patients CTA expression was detected in TFL, which was a negative independent prognostic factor for HCC-recurrence (hazard ratio [HR] 2.28; $p = .003$) and HCC-specific survival (HR 2.51; $p = .026$) after resection. See Figure for the Kaplan Meier curves.
Up to now six CTAs have been tested for immunogenicity. Ten out of fourteen HCC patients displayed CD4 and/or CD8 T-cell responses

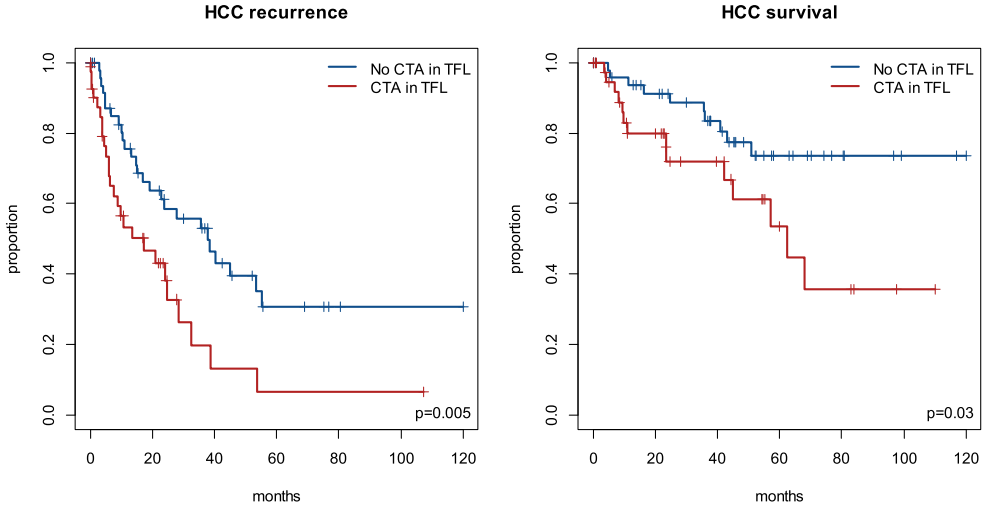

Figure: (abstract: AS049)

against one or multiple CTAs, and all CTAs induced a T-cell response in at least one patient. MAGE-A1 and MAGE-C2 most frequently invoked T-cell responses, both in 5 patients.
Conclusion: In this comprehensive study, we established a panel of 12 testis-restricted CTAs which are expressed in almost 80% of HCC tumors. The negative association between expression of these CTAs in TFL and HCC-recurrence and -survival shows the relevance of targeting of these antigens. Preliminary immunogenicity tests show that the 6 examined CTAs are immunogenic. In HCC, immunotherapeutic strategies targeting these CTAs may therefore be a valuable addition to currently available immunotherapies like checkpoint blockade, to improve systemic anti-tumor immunity.

AS050

Regorafenib versus nivolumab after sorafenib failure: real-world data in patients with hepatocellular carcinoma

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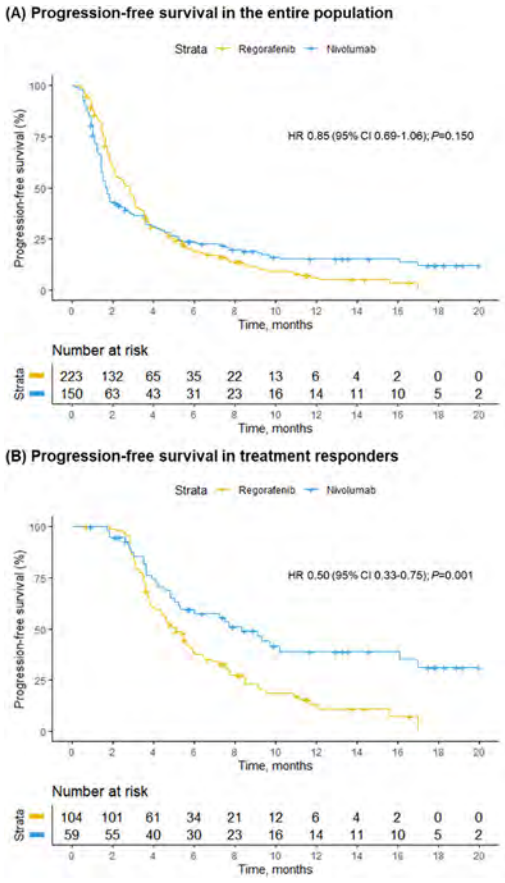
Background and Aims: Regorafenib and nivolumab are drugs approved for second-line treatment of patients with hepatocellular carcinoma (HCC) after sorafenib failure. However, the effectiveness of regorafenib and nivolumab following sorafenib has not been directly compared in a real-world clinic setting.
Method: This study retrospectively evaluated 373 patients with HCC who were treated with regorafenib (n = 223) or nivolumab (n = 150) as a second-line treatment after sorafenib failure between July 2017 and February 2019.



Results: Progression-free survival (PFS; hazard ratio [HR], 0.85; 95% confidence interval [CI], 0.69–1.06; P = 0.150), time to progression (TTP; HR, 0.95; 95% CI, 0.77–1.19; P = 0.680), and overall survival (OS; HR, 0.83; 95% CI, 0.64–1.07; P = 0.154) did not differ significantly between groups of patients treated with regorafenib and nivolumab, findings consistently observed by multivariable-adjusted, propensity score-matched, and inverse probability treatment weighting (IPTW) analyses. However, the objective response rate was significantly higher in the nivolumab than in the regorafenib group (13.3% vs, 4.0%; P = 0.002). When the effectiveness of regorafenib and nivolumab was compared in treatment responders, defined as patients who achieved complete response, partial response, or stable disease after first response evaluation, PFS (HR, 0.50; 95% CI, 0.33–0.75; P = 0.001), TTP (HR, 0.48; 95% CI, 0.31–0.73; P < 0.001), and OS (HR, 0.51; 95% CI, 0.31–0.87; P = 0.013) were significantly longer in the 59 responders to nivolumab than in the 104 responders to regorafenib, findings also observed by multivariable-adjusted and IPTW analyses.
Conclusion: Survival outcomes in patients treated with regorafenib and nivolumab after sorafenib failure did not differ significantly. However, nivolumab may be more effective than regorafenib in treatment responders.

AS051

Identification of neoantigen-reactive T cells in hepatocellular carcinoma: implication in adoptive T cell therapy

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Background and Aims: Emerging evidence has suggested that neoantigens (NeoAgs) play a critical role in antitumor immune response. Tumor-infiltrating T lymphocytes (TILs) specific for NeoAgs have been identified in patients with high mutational load (ie: melanoma), but also in tumor with intermediate mutational load, such as cholangiocarcinoma. Hepatocellular carcinoma (HCC) ranks in the group of tumors with moderated mutation load but evidence for the existence of neoAgs-specific TILs is still lacking. Our aim was to investigate if patients with HCC harbor T lymphocytes that recognize neoAgs expressed by autologous tumors.
Method: Whole exome (WES) and transcriptome (RNAseq) sequencing of tumor lesions and normal tissues were performed in 4 HCC patients submitted to surgery. Somatic variants, including single nucleotide variants (SNVs) and indels, were analyzed using a bioinformatic pipeline that incorporates 4 variant callers and data from WES and RNAseq. All somatic variants, independent of prediction algorithms, were tested for TIL recognition. For each patient, we generated multiple TIL cultures from tumor fragments. To determine if any of the TIL cultures specifically recognized the mutant gene products (25 amino acid peptides containing the mutant amino acids), autologous antigen presenting cells were transfected with tandem minigenes (encoding all the mutations) or pulsed with synthetic peptide pools (containing the mutations) and then co-cultured with TILs. The specific T-cell response was evaluated by ELISPOT of IFNγ and detection of CD137 by flow cytometry.
Results: WES and RNAseq analysis of the tumor lesions revealed variable numbers of non-synonymous somatic mutations, ranging

from 11 to 78 mutations. SNVs were the most common mutation types (93%). Interestingly, CD4+ TILs from the patient harboring the highest number of somatic mutations recognized patient's specific neoAgs, as determined by both ELISPOT assay and upregulation of CD137 molecule. We are currently working on the further characterization of these neoAg-specific TIL populations.
Conclusion: This finding suggests that neoAg-reactive TILs reside in HCC and provides a rationale for the future use of adoptive T cell therapy targeting neoAgs in this tumor. Fundings by Gobierno de Navarra Salud (45/2017).

AS052

PD1Hi CD103+ CD8+ T cells with exhausted-like Trm features promote tumor progression, but predict a favorable response to anti-PD1 treatment in hepatocellular carcinoma

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Background and Aims: Tissue resident memory cells (TRM) define a subset of T cells commitment to their tissue of residence. Conventional identified TRM cells exhibit higher levels of expression effector cytokines that are thought to provide potent front line defense against infectious diseases and carcinomas. While recently exhausted TRM cells have been reported to involved in immune balance of some infectious diseases. So, the features of TRM cells are far from elaborated and its role in hepatocellular carcinoma (HCC) remains elusive.
Method: Forty-four paired peripheral blood, nontumor tissues and HCC specimens from patients received surgical resection were obtained to identify the phenotype features, functional state and clinical significance of TRM cells. In addition, the formation and maintenance of exhausted TRM cells were explored in vitro. Furthermore, the association between TRM cells and anti-PD1 treatment efficacy was determined in HCC patients.
Results: We identified a novel subset of tumor- infiltrated CD8 +CD103+ T cells that coexhibit exhaustion and tissue residence features. These exhausted-like TRM cells exhibited high levels of PD1 and other immune check points (Tim3, LAG3) with inferior expression effector cytokines of IFN-g and TNF-a. Persistent TCR stimulation in HCC environment was crucial for exhausted PD-1^{hi} CD103+ T cells induction, which can be abolished by inhibiting MAPK signals mediated autophagy. Furthermore, exhausted-like TRM cells can be further reinvigorated by PD1 blockade in vitro and predict a favorable response to Anti-PD1 therapy in HCC patients.
Conclusion: PD1^{hi}TRM cells were accumulated in HCC but exhausted that invades anti-tumor immunity. Exhausted TRM cells can be further reinvigorated by PD1 blockade and might initiate a favorable response to Anti-PD1 therapy in HCC patients.

AS053

Cabozantinib enhances the efficacy and immune modulatory activity of anti-PD1 therapy in a syngeneic mouse model of hepatocellular carcinoma

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Background and Aims: Immune checkpoint inhibitors (ICPIs) including anti-PD1 therapies have shown promising results for the treatment of hepatocellular carcinoma (HCC), however responses are only observed in a subset of patients (15–20%). Cabozantinib is an FDA-approved tyrosine kinase inhibitor with anti-angiogenic, anti-proliferative and immune-stimulatory activity, thus potentially promoting a switch among immunologically "cold" tumours towards a favourable "hot" immune profile and improved responses to ICPIs. Here we aimed to assess the anti-tumour effects and mechanism of action of cabozantinib alone and in combination with anti-PD1 treatment in an immunocompetent murine model of HCC.
Method: C57BL/6J mice bearing subcutaneous Hepa1-6 tumours (200–300 mm^3) were randomised to receive anti-PD1 or placebo IgG (10 mg/kg *i.p.* every 3 days for a total of 5 doses) ± cabozantinib (30 mg/kg daily *p.o.*) (20 mice per treatment). Six mice per arm were culled after the last anti-PD1 dose and 2 hours after cabozantinib administration (day 14 of treatment). The remaining mice were sacrificed at study termination (day 32). Blood and tumour samples were collected for histological and molecular analyses, immune cell characterisation by flow cytometry, and cytokine profiling using a multiplex assay.
Results: Both cabozantinib and anti-PD1 monotherapies significantly reduced tumour growth or induced tumour regression compared to placebo ($p < 0.05$). Combination treatment exhibited the greatest anti-tumour effect, inducing the highest objective response rate (79%) and shortest time to objective response (7 days, $p < 0.03$ *vs.* placebo). Histological examination revealed that cabozantinib and combination-treated tumours had significantly reduced viable tissue volumes ($p < 0.001$) and higher rates of necrosis ($p < 0.01$) compared to placebo. Flow cytometry analysis revealed increased proportions of tumour-infiltrating neutrophils, lower proportions of tumour-infiltrating exhausted CD8+ T cells, and higher overall proportions of circulating T lymphocytes in cabozantinib and combination-treated animals ($p < 0.05$). Furthermore, significantly increased circulating memory/effector T cell proportions were observed in combination-treated mice ($p < 0.05$ *vs.* placebo). Peripheral blood profiling of 31 cytokines revealed changes including increases in the T lymphocyte chemo-attractants IL-16 and CCL27 in combination-treated mice compared to placebo ($p < 0.05$). Gene expression and IHC analyses of tumour samples are ongoing.
Conclusion: Cabozantinib increased the response rate to anti-PD1 therapy and had beneficial immunomodulatory activity in our syngeneic model, thus supporting further investigation into combining cabozantinib and anti-PD1 for the treatment of HCC.

AS054

Treatment-related toxicity predicts for improved outcome in patients with hepatocellular carcinoma (HCC) treated with immune checkpoint inhibitor therapy

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Background and Aims: Reversal of cancer immune-tolerogenesis with immune checkpoint inhibitors (ICI) is an emerging therapeutic modality in HCC, although the precise molecular mechanisms underscoring ICI efficacy are poorly understood. The development of treatment-related adverse events (trAE) favourably influences outcome in ICI recipients. In this multi-center study we aimed to verify its prognostic role in HCC.
Method: We established an international consortium of 9 tertiary referral centres located in Europe (n = 68), United States (n = 226) and Asia (n = 47) to derive a prospectively maintained cohort of 341 patients who underwent ICI treatment. We tested whether the development of clinically significant trAE (ie. graded >2) predicted for improved overall response rates (ORR) and overall (OS), using time-dependent survival analyses.
Results: Of 331 eligible patients, 254 (76%) had Barcelona Clinic Liver Cancer stage C HCC, 233 were cirrhotic (70%) mostly due to Hepatitis C infection (n = 129, 39%). Patients had received at least 1 line of prior systemic therapy (n = 297, 90%) before anti-PD-1/PD-L1 ICI mono-therapy (n = 280, 85%) or combinations (n = 51, 15%). Median OS was 12.1 months (95%CI 9.2–15 months) and ORR was 19% with 23 complete (6%) and 42 partial responses (13%). Overall, 133 patients (40%) experienced at least 1 trAE. Seventy were of grade >2 (21%), most frequently affecting the liver (n = 24, 7%). Permanent ICI discontinuations were secondary to disease progression (n = 160, 48%) or unacceptable toxicity (n = 12, 4%).
Emergence of trAEs graded >2 whilst on ICI predicted for improved OS (median 19.7 versus 11.0 months, Hazard Ratio [HR] 0.32, 95%CI 0.16–0.65, p = 0.001) and increased ORR (30% vs. 16%, Chi-square 5.9, p = 0.01). Other univariable prognostic factors included AFP>400 ng/mL (HR 1.49 95%CI 1.1–2.0, p = 0.01), Child Pugh Class (B vs. A, HR 2.74, 95%CI 1.8–4.0, p < 0.0001) and geographical origin (Europe vs. Asia HR 0.50 95%CI 0.27–0.92, p = 0.02). Following time-dependent Cox regression analyses, the occurrence of trAEs remained a predictor of improved OS (HR 0.39, 95%CI 0.16–0.92, p = 0.03) independent of Child Pugh Class (HR 1.99, 95%CI 1.18–3.35, p = 0.009), BCLC stage (p = 0.43), AFP levels (p = 0.11), geographical origin (p = 0.67) corticosteroid therapy (p = 0.54) and type of immunotherapy regimen received (monotherapy vs. combination, p = 0.58).
Conclusion: This is the first study to demonstrate that trAEs may influence response and survival in patients with HCC receiving ICI. Mechanistic studies highlighting the immune-biologic foundations of such relationship are warranted.

Immune-mediated and chronic cholestasic liver disease: Experimental and pathophysiology

AS055

Co-culture of bile-derived organoids from primary sclerosing cholangitis patients with CD4+ T cells replicates pathogenic, CCL20 dependent biliary-immune interactions

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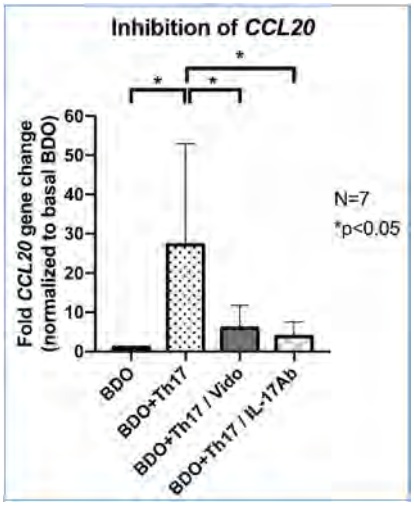
Background and Aims: The difficulty in obtaining primary cholangiocytes has limited advances in Primary Sclerosing Cholangitis (PSC). We recently reported that human PSC Bile-Derived Organoids (BDOs) exhibit biliary cell features and an inducible reactive inflammatory phenotype (Soroka et al Hepatology 2018). This suggests that BDOs can be used for biliary-immune studies, however co-culture testing has not been reported. We studied human PSC BDO/T-cell interactions and inhibition of pathogenic inflammatory signaling.
Methods: Transwell migration assays were performed with healthy control CD4+ T-cells activated by CD3/CD28 crosslinking and conditioned culture supernatants from PSC BDO stimulated with IL-17A or TNF-alpha. Naïve control CD4+ T-cells were co-cultured with unstimulated BDOs for 48 hrs. CD4+ T-cells were differentiated to a Th17 phenotype then co-cultured with unstimulated BDOs for 48 hrs ± anti-IL17 Ab or vidofludimus (Vido), a T-cell inhibitor. BDO genes were analyzed by RT-qPCR, cytokine secretion by ELISA, and T-cell activation by FACS.
Results: BDOs stimulated with IL-17A or TNF-alpha significantly increased CCL20 secretion vs. unstimulated BDOs (IL-17A: 41,764; TNF-alpha: 167,763; unstimulated: 7,095 pg/mL, p < 0.005). Transwell migration assays showed that significantly more activated (CD69+) T-cells migrated toward supernatants from IL-17A (1.27-fold) and TNF-alpha (1.55-fold) stimulated vs. unstimulated BDOs (p < 0.05, p < 0.005, respectively). Co-culture of unstimulated BDOs with naïve CD4+ T-cells revealed that some BDOs can directly induce the T-cell activation marker CD69. Furthermore, co-culture of unstimulated BDOs with Th17 cells revealed a significant increase in BDO *CCL20* expression (30-fold) and CCL20 secretion (11.5-fold) compared to BDOs without Th17 cells (p < 0.05 for each). Importantly, gene expression and protein secretion of CCL20, and of IL-17A, were significantly reduced (80–85%) by anti-IL17A Ab and by Vido, suggesting that the inflammatory recruitment signaling by BDOs can be inhibited in an IL-17 dependent manner (Figure).



Conclusions: BDOs from PSC patients can activate and induce migration of CD4+ T-cells, while co-cultured Th17 cells induce reactive gene expression and secretion of BDO-derived inflammatory molecules. This supports the hypothesis that Th17 cells damage biliary epithelia through CCL20 inflammatory responses in PSC. BDOs are a novel technology to study pathogenic biliary-immune cell interactions, and a personalized drug-testing platform in human PSC.

AS056

Protective effects of MBT-1805 on alpha-naphthalene isothiocyanate induced cholestasis animal model

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Background and Aims: Primary biliary cholangitis (PBC) is an immune-related liver disease with unclear mechanism. UDCA is currently the preferred treatment, with inadequate response in some

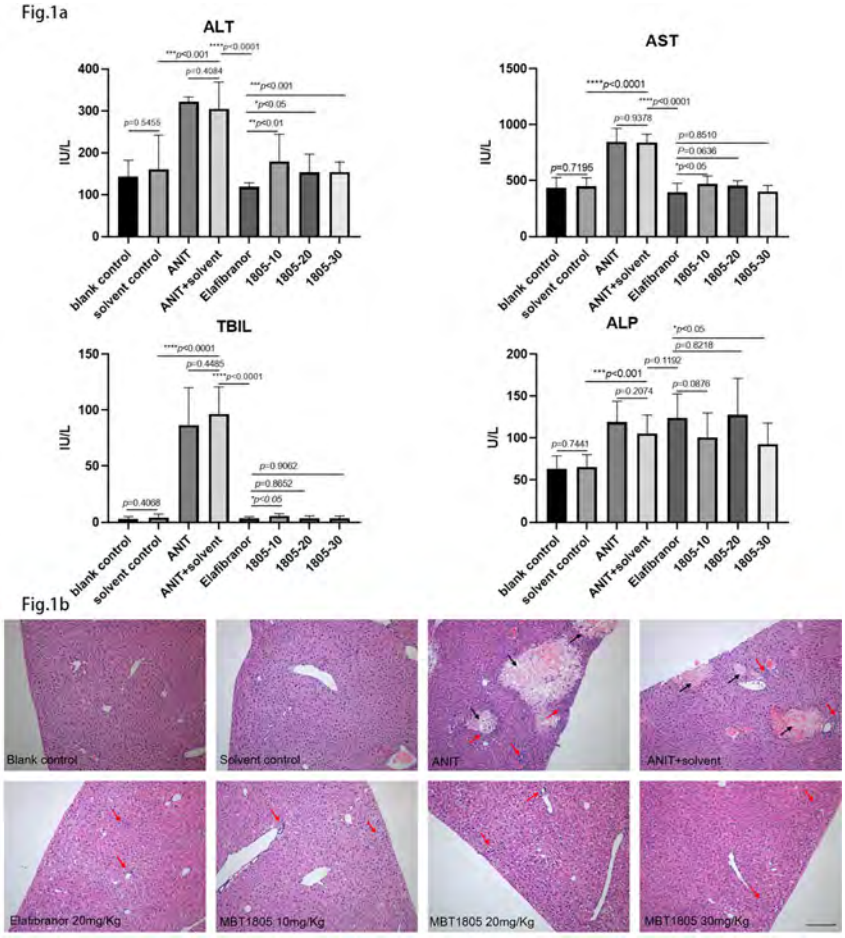

Figure 1a: (abstract: AS056): Serological testing. 1b. Pathologic results. Black arrows for necrosis, red arrows for inflammation infiltration. (scale bar: 400 μm).

patients. ANIT (alpha-naphthalene isothiocyanate) can lead to liver injury and rapid cholestasis. We verified the effects of newly developed MBT-1805 on ANIT-induced cholestasis compared with Elafibranor. MBT-1805 is a novel drug candidate built on resveratrol scaffolds and it is the most balanced PPAR-α/γ/δ agonist with moderate activity (EC_{50}: 8.46 μM, 11.94 μM, 11.5 μM respectively).
Method: Eight groups of C57BL/6J mice (8 weeks) were raised in SPF environment, with 10 mice each group. The mice were pretreated suitable dose of drugs for 7 days before ANIT administration by gavage. Experiment was terminated after ANIT administration (75 mg/Kg) for 24 hours. We recorded the body weight before administration and before mice sacrificed, as well as the weight of liver, spleen and gallbladder after organs isolation. Serum was collected for testing ALT, AST, TBIL and ALP. HE staining of liver tissues were also detected.
Results: All experimental mice survived. Severe liver injury occurred in ANIT/ANIT+solvent treated mice. Levels of ALT, AST, TBIL, ALP ($p < 0.05$,Fig. 1a) and weight of gallbladder ($p < 0.0001$) were elevated obviously compared with blank/solvent control groups. The above indicators in mice of Elafibranor group (20 mg/Kg) improved, except ALP ($p = 0.1192$). All groups of MBT1805 (10 mg/Kg, 20 mg/Kg and 30 mg/Kg) showed perfect efficiency on protecting mice from injury of ANIT, and efficiency showed dose-dependent. Particularly, 30 mg/Kg group was more effective than Elafibranor in reducing ALP. ($p < 0.05$,Fig. 1a). Pathological results also showed good protective effects, no obvious necrosis and less inflammation infiltration were observed in all groups of MBT-1805 treated mice. 30 mg/Kg group showed less inflammation infiltration than Elafibranor particularly (Fig. 1b).
Conclusion: The newly developed MBT-1805 showed good protective effects on ANIT-induced cholestasis, and efficiency showed dose-dependent. 30 mg/Kgof MBT-1805 performed better compared with Elafibranor.

AS057

Transcriptome and colocalisation analysis of CCR9+ gut-homing T cells and other immune cells identifies important genes and biological pathways potentiating primary sclerosing cholangitis risk

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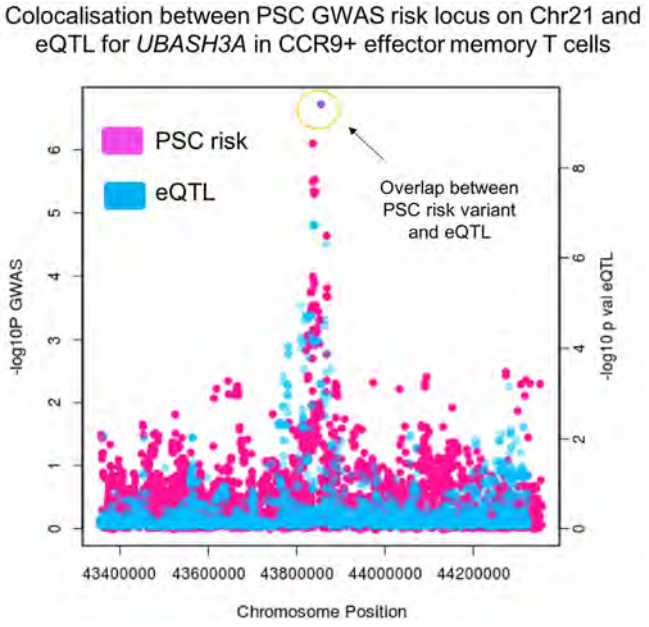
Background and Aims: 23 regions of the genome have been associated with primary sclerosing cholangitis (PSC) risk. The majority are in non-coding regions, and identifying the affected genes and cell-types remains a major hurdle in translating these genetic associations into therapeutic targets. We, and others, have shown that identifying cis-eQTLs (genetic variants that affect expression level of a nearby gene) that share causal variants with disease risk loci (colocalise) can identify genes, cell-types and

mechanisms underlying complex disease risk. However, identifying disease-relevant eQTLs is challenging as some are only active in specific cell-types or activation states and have no observable impact on gene expression in naïve cells.

Method: We generated eQTL maps for six T-cell subtypes, including rare CCR9+ gut-homing T-cells hypothesised to be pathogenetic in PSC, derived from peripheral blood of 80 donors with PSC. We analysed our PSC-specific T-cell eQTL maps alongside existing eQTL maps for other immune cells, in total covering >12 immune cell types and >10 different activation states. We called cell-type-specific and shared eQTLs using *MashR*. To identify genes and cell-types perturbed in PSC we performed Bayesian tests of colocalisation across PSC risk loci and eQTLs for all cell-types.

Results: We identified >9000 eQTLs across our PSC-specific T-cell subsets at 5% FDR, many clustered within pathways involved in inflammation and immune-modulation. Approximately 15% of eQTLs were specific to a single PSC T-cell-subtype. Colocalisation analysis confirmed the importance of CCR9+ and CCR9- effector memory T-cells and CD14+ monocytes in PSC pathogenesis, as 12 PSC risk loci colocalised with >1 eQTL with a posterior probability >80% in at least one of these cell-types.

Some PSC-risk loci were highly specific to a single cell-type. For instance, the Chr21 PSC risk locus colocalised with an eQTL for *UBASH3A*, a gene potentiating IL-2 secretion, across all T-cell subtypes (including CCR9+ T-cells), from donors with and without PSC. In contrast, other risk loci affected the same gene across several different cell-types; e.g. the Chr19 risk locus colocalised with an eQTL for *PRKD2* in monocytes, neutrophils and T-regs. Interestingly, we observed several PSC-risk loci, for which the affected gene differed per cell type. One such region was the Chr11 PSC locus which colocalised with an eQTL for *CCDC88B* in CD14+ monocytes and neutrophils, but colocalised with an eQTL for lncRNA *AP003774.2* in B-cells, PSC T-regs and CCR9+ effector memory T-cells but not in T-cells from healthy donors.



Conclusion: Our analyses confidently identify the genes and cell-types affected by multiple PSC-risk loci, forming the basis for further functional follow-up and bringing us closer to drug-target discovery.

AS058

Double resin casting micro computed tomography (CT) reveals biliary and vascular pathology in tandem in a mouse model for alagille syndrome

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Background and Aims: Malformation of lumenized structures, such as the intrahepatic circulatory or biliary systems, is a hallmark of several liver disorders, from vascular hepatic disease to Alagille syndrome. Liver architecture in mice has typically been studied using 2D sections and, more recently, with thicker tissue sections and whole mount immunofluorescence, neither of which resolves 3D architecture adequately. Importantly, the vascular and biliary systems are inter-dependent, and we therefore aimed to develop a robust method to image, digitalize and quantify 3D architecture of the biliary and vascular systems in tandem.

Method: The biliary and portal vein trees of the mouse liver were injected with Microfil resin, followed by microCT scanning. Tomographic data was segmented and analyzed using a MATLAB script we wrote to investigate length, volume, tortuosity, branching, and the relation between the vascular and biliary systems. We applied this pipeline (Double resin casting micro computed tomography (DUCT)) to a mouse model for Alagille syndrome ($Jag1^{Ndr/Ndr}$ mice), in which the biliary system is absent at postnatal stages, but regenerates by adulthood. Phenotypes discovered using DUCT were validated with cumbersome consecutive liver sections from mouse. Phenotypes identified using DUCT, and confirmed in sections of mouse liver, were further validated in liver samples from patients with Alagille syndrome.

Results: DUCT revealed tortuous bile ducts either placed further from portal veins, or ectopically traversing the parenchyma and connecting two portal areas, in $Jag1^{Ndr/Ndr}$ mice. Furthermore, bile ducts either ended abruptly, or branched independently of portal vein branching, with bifurcations placed hilar or peripheral to portal vein branches. Branch lengths were stochastic in $Jag1^{Ndr/Ndr}$ mice, with shorter hilar branches, suggesting ectopic regenerative sprouting occurs in the hilar region. The branching defects, parenchymal bile ducts, and blunt endings were confirmed in samples from patients with Alagille syndrome.

Conclusion: DUCT is a powerful technique that provides 3D reconstruction of resin-cast networks and quantification of 3D architecture. It exposes and quantifies previously unknown vascular and biliary phenotypes in mouse models, and thus can reveal new phenotypes in patients. Application of this technique to mouse models of liver disease will improve and standardize our 3D understanding of healthy and pathological liver states.

AS059

The anti-inflammatory receptor TREM2 protects the liver from cholestatic injury

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Background and Aims: Cholestasis is a common feature of different cholangiopathies such as PBC and PSC. This condition causes liver inflammation and injury in epithelial cells, thereby inducing a specific wound healing response which involves ductular reaction, activation of kupffer cells (KCs), hepatic stellate cells (HSCs) and immune cells, finally leading to biliary fibrosis. In this regard, bacterial components that translocate to the liver act as pro-inflammatory signals, binding to toll-like receptors, thus promoting disease progression. Importantly, our group and others have reported that the triggering receptor expressed on myeloid cells 2 (TREM2) inhibit TLR-mediated signaling. This study aims to evaluate the role of TREM2 in cholestasis.
Method: *TREM2* expression was analyzed in the liver of patients with PBC and PSC and in mouse models of cholestasis, compared to healthy livers. Wild type (WT) and *Trem-2* knockout (*Trem2*$^{-/-}$) mice were subjected to bile duct ligation (BDL), or sham operated. In parallel, WT and *Trem2*$^{-/-}$ mice were treated with an antibiotic cocktail and then subjected to BDL. *In vitro*, *TREM2* was experimentally overexpressed in human hepatic stellate cells and inflammatory and fibrotic responses were analyzed. Effects of the treatment with bile acids in TREM2 expression in human hepatic stellate cells were assessed.
Results: *TREM2* expression is upregulated in the liver of patients with PBC and PSC as compared to controls; this receptor is also upregulated in murine models of cholestasis. Interestingly, TREM2 expression in patients positively correlated with inflammatory, fibrotic and cholestatic markers. *Trem2*$^{-/-}$ mice showed augmented biliary expansion after BDL. Likewise, *Trem2*$^{-/-}$ livers displayed enhanced profibrogenic (*Col1a1*) and hepatic stellate cell activation marker (*Acta2*) expression. *Trem2*$^{-/-}$ livers also exhibited enhanced pro-inflammatory marker expression (*Tnf, Mcp1, Cxcl1*) and augmented neutrophil recruitment into the liver as detected by NIMP-R14 inmunohistochemistry. This was accompanied by enhanced necroptotic cell death, while no differences were detected in apoptosis. Treatment with antibiotics abolished some of the effects observed in *Trem2*$^{-/-}$ mice after BDL. *In vitro*, *TREM2* overexpression in LX-2 cells leads to diminished profibrotic *(ACTA2, COL1A1, FIBRONECTIN)* and pro-inflammatory (*TNF* and *MCP1*) gene expression. Interestingly, treatment with UDCA induced *TREM2* expression in these cells.
Conclusion: TREM2 is overexpressed in the liver of patients with PBC and PSC and during experimental cholestasis. TREM2 acts as a negative regulator of inflammatory responses during cholestatic injury in mice. On the other hand, UDCA increases *TREM2* expression in HSCs, suggesting this could be and additional hepatoprotective mechanism of UDCA in cholestasis.

AS060

24-nor-ursodeoxycholic acid ameliorates intestinal inflammation by counteracting Th17/Treg imbalance via redirecting mTOR metabolic sensing programs in CD4+ T cells

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Background and Aims: 24-nor-ursodeoxycholic acid (*nor*UDCA) is a novel therapeutic bile acid for treating primary sclerosing cholangitis (PSC) which is strongly associated with inflammatory bowel disease (IBD). Th17/Treg imbalance is a key immunopathological factor driving PSC-IBD. We hypothesized that *nor*UDCA has immunomodulatory potency on Th17/Treg balance contributing to its therapeutic efficacy besides previously established effects in CD8$^+$ T cells. Since Th17/Treg lineage determination is controlled by metabolic reprogramming in activated CD4$^+$ T cells, we aimed to explore how *nor*UDCA affects CD4$^+$ T cell metabolic sensing programs and Th17/Treg balance.
Method: *nor*UDCA effects on CD4$^+$ T cell development and Th17/Treg balance were assessed by *in vitro* proliferation and differentiation assays, as well as in the model of CD25$^-$CD45RB^{high}CD4$^+$ T cell induced colitis, a Th17 cell driven experimental IBD model.
Results: *In vitro*, *nor*UDCA reduced CD4$^+$ T cell proliferation and lymphoblast formation by 46.8% (vs control, $p < 0.05$). *nor*UDCA inhibited Th17 cell differentiation while promoting FoxP3 expression. Mechanistically, *nor*UDCA suppressed mTORC1 and mTORC2 kinase activities as reflected by lower phosphorylation level of P70 S6 Kinase(Thr421/Ser424) and pAKT(Ser473) by 40.7% ($p < 0.005$) and 51.2% ($p < 0.05$), respectively. Consequently, *nor*UDCA decreased gene expression of mTOR regulated glycolytic enzymes, such as hexokinase2 and lactate dehydrogenase A ($p < 0.05$) and subsequently reduced glycolysis in developing CD4$^+$ T cells with lower extracellular acidification rate. Conversely, fatty acid oxidation was enhanced by *nor*UDCA as indicated by increased gene expression of *Cpt1alpha* ($p < 0.005$). Supporting *in vitro* data, *nor*UDCA reduced CD4$^+$RORγt$^+$ T cells in intraepithelial mucosa ($p < 0.05$), while expanded CD4$^+$CD25$^+$Foxp3$^+$ Tregs in spleen ($p < 0.05$), intraepithelial mucosa ($p < 0.05$) and lamina propria ($p = 0.0635$) after colitis induction. *nor*UDCA induced-Tregs demonstrated immunosuppressive functions *in vivo* as evidenced by reduced frequencies of CD4$^+$ T cells expressing IL17A/IFNgamma and IL17A/IL22 in intraepithelial mucosa, lamina propria and mesenteric lymph nodes and improved colon immunopathology.
Conclusion: *nor*UDCA redirects mTOR-associated metabolic sensing programs in activated CD4$^+$ T cells to counteract Th17/Treg imbalance, indicating *nor*UDCA may represent a promising immunometabolic drug for treating T cell based inflammatory diseases, such as PSC.

Assessing the burden of liver disease

AS061

Increasing burden of cirrhosis projected to 2040 in Canada: implications for prevention, screening, and management

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Background and Aims: Disease burden related to cirrhosis varies by etiology and age with a recent increase evident in younger generations. The aim of this study was to describe the incidence of cirrhosis by etiology and birth cohort and estimate future cirrhosis burden to guide future intervention efforts.
Method: Retrospective population-based cohort study using provincial healthcare data from Ontario, Canada from 2000–2017. Adults with incident cirrhosis were identified using a validated case definition and described by year of birth. Cirrhosis etiology was assigned to one of five categories as either hepatitis B (HBV), hepatitis C (HCV), non-alcoholic fatty liver disease (NAFLD)/cryptogenic, alcohol-related liver disease (ALD), or Other using a validated hierarchical algorithm, incorporating results of viral hepatitis testing, and administrative diagnostic codes. Annual age and sex adjusted cirrhosis incidence was calculated per 100,000 person-years standardized to the 2011 Canadian population overall and stratified by etiology and birth cohort. Projected annual incidence rates of cirrhosis were calculated based on Ontario population projections to the year 2040 using age-period-cohort analysis and cubic splines.
Results: 159,549 incident cases of cirrhosis were identified (59% male, median age 57 years [IQR 47–68], 53% NAFLD/cryptogenic, 25% ALD, 12% HCV, 6% HBV, 5% Other). The overall incidence of cirrhosis increased in all birth cohorts (Figure A). However importantly, these trends varied by both birth cohort and etiology (Figure B–F). For NAFLD/cryptogenic cirrhosis, the incidence is projected to increase in all birth cohorts (Figure B); rates for ALD are expected to increase only in cohorts born after 1965 (Figure C), rates of HCV cirrhosis are projected to decline for all birth cohorts except those born >1980 (Figure D), while the incidence for both HBV and Other causes are projected to decline or stabilize for all cohorts (Figure E and F).
Conclusion: Without intervention by 2040, 73% of all new diagnoses of cirrhosis will be secondary to NAFLD, 20% from ALD, and 5% from HCV. Although NAFLD will be the primary driver of these trends, our results highlight the significant contribution of both ALD and HCV in birth cohorts after the baby boomers. Wide-scale public health, lifestyle, and pharmacologic interventions are needed in order to potentially reverse these trends, especially in young adults.

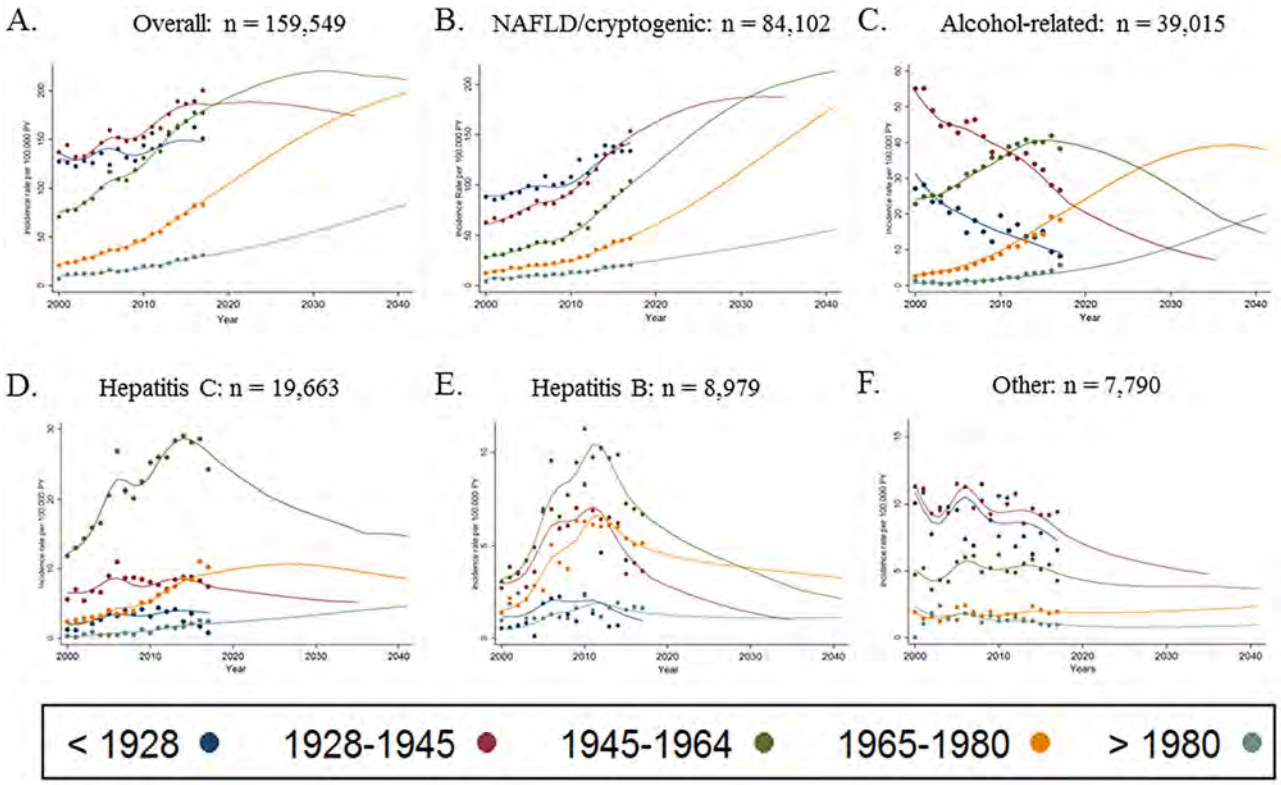

Figure: Calculated (dots) and projected (lines) age and sex standardized incidence rates of cirrhosis by birth cohort in Ontario, Canada. A: all etiologies; B: non-alcoholic fatty liver disease/cryptogenic; C: alcohol-related; D: hepatitis C; E: hepatitis B; F: Other (includes autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cholangitis, Wilson disease, alpha-1 antitrypsin deficiency, hemochromatosis.

Figure: (abstract: AS061)

AS062

The progression of liver disease in 69,290 individuals in Wales from 1999–2019: tracking the evolution of liver disease

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Background and Aims: Major epidemiological studies of liver disease to date are based upon mortality data limiting our understanding of morbidity on a population scale. We established a Wales Liver Disease registry to understand the true burden and progression of liver disease.

Method: The registry is populated by ICD10 code diagnoses for Welsh residents derived from Office of National Statistics mortality data and inpatient/day case activity derived from NHS Wales Informatics Service Patient Episode Database for Wales between 1999–2019. Pseudo-anonymised linkage of i) causative diagnoses, ii) cirrhosis, iii) portal hypertension, iv) decompensation and v) liver cancer codes enabled tracking the progression of liver diseases.

Results: The population of Wales is 3.1 million, 69,290 individuals were diagnosed with liver disease between 1999–2019. There were 16,990 (24.5%) diagnoses of cirrhosis, 12,860 (18.6%) with portal hypertension, 10,400 (15%) with hepatic failure/decompensation and 6055 (8%) with liver cancers and mortality reached 53% (36,770 died). The incidence of alcohol liver disease (ALD), chronic viral hepatitis and non-alcoholic fatty liver disease (NAFLD) increased 1.23, 1.7 and 10-fold respectively. NAFLD is now the predominant cause of liver disease in Wales (incidence 1894 in 2018–19).

Progression of liver disease over 10 years was assessed in 25,390 individuals with an initial inpatient diagnosis between 1999–2009. Progression and mortality were more marked in ALD (cirrhosis 41.7%, decompensation 25% and liver cancer 2.4%, mortality 79%) than NAFLD (cirrhosis 11%, decompensation 8% and liver cancer 2%, mortality 46%) and HCV (cirrhosis 15%, decompensation 8% and liver cancer 5%, mortality 29%).

Conclusion: Liver disease in Wales is increasing. Whilst ALD is associated with increased disease progression, the marked increase in NAFLD incidence indicates that the modest conversion to decompensation will cause significantly increased mortality and morbidity.

The progression of 7374 patients diagnosed with alcoholic liver disease between 1999 and 2009 in Wales over the following 10 years. Vertical bars demonstrate stage of disease (red = ALD diagnosis 100%, dark blue = cirrhosis 41.7%, light green = portal hypertension/portal vein thrombosis (PH/PVT) 32%, orange = decompensation 25%, light orange = liver cancer 2.4%, dark green = survival 21%, light blue = death 79%). Blocks of horizontal colour between bars demonstrate the flow of individuals moving to later stages of disease and mortality or survival at 10 years post diagnosis. Light blue progression to mortality, dark blue progression to cirrhosis, light green progression to PH/PVT, orange progression to decompensation, light orange progression to liver cancer and dark green survival to follow up end point. Black dot indicates HCC diagnosis precedes decompensation.

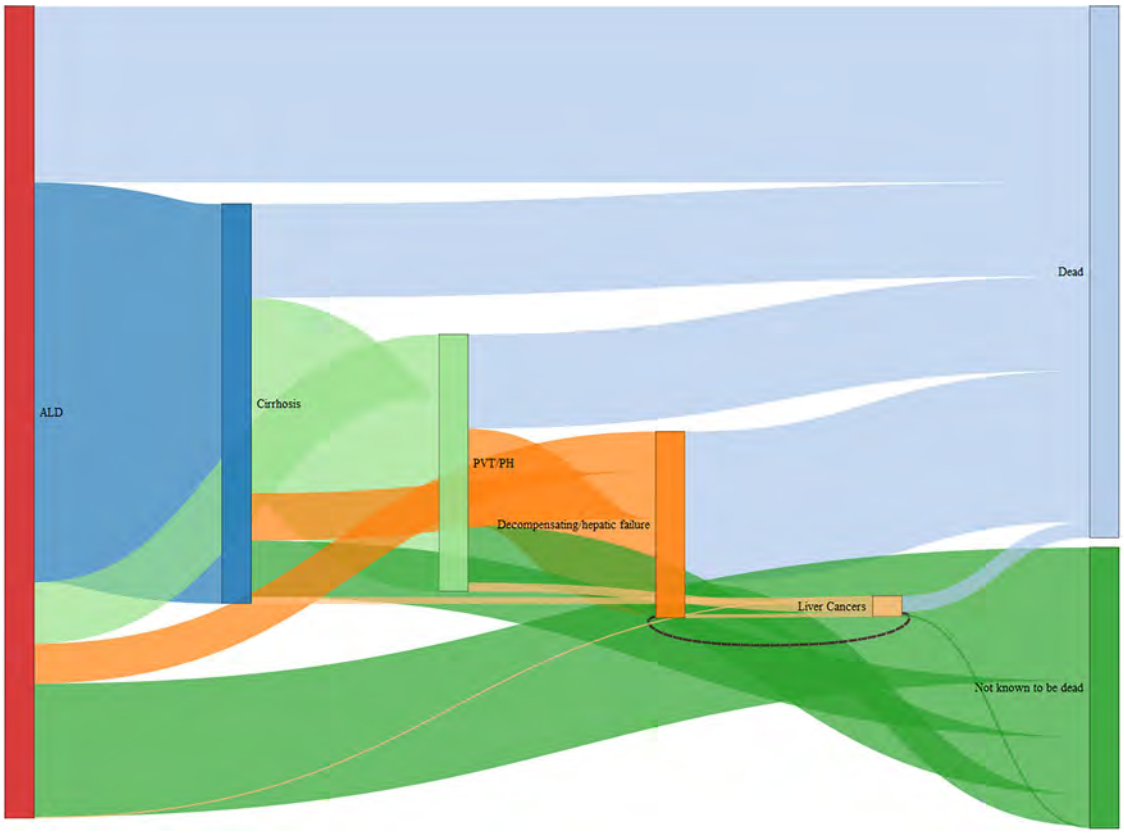

Figure: (abstract: AS062)

AS063

The growing burden of disability related to non-alcoholic fatty liver disease: data from global burden of disease 2007–2017

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Background and Aims: Although chronic liver disease (CLD) is an important cause of mortality worldwide, data on CLD-related morbidity and disability is not widely available. Our aim is to assess the global burden of disability associated with complications of CLD [primary liver cancer (LC) and cirrhosis] according to the most common causes of liver disease from 2007 through 2017.
Method: The Global Burden of Disease (GBD) study estimation methods were used to assess years lost due to disability (YLD), years of life lost (YLL) and disability-adjusted life-years (DALYs), obtained from the GBD 2017 study. Results were presented at 21 GBD regions as well as 195 countries. Temporal trends were assessed by percent change from 2007 through 2017.
Results: In 2017, there were 6.1 million worldwide incident cases of CLD (15.6% LC and 84.4% cirrhosis), 2.14 million liver-related deaths (38.3% LC and 61.6% cirrhosis) which contributed to 62.16 million DALYs (33.4% LC and 66.5% cirrhosis). The majority of DALYs from CLD was attributed to years of life lost (96.8%) and only 3.2% from years of life lived with disability. The highest age-standardized-years-of-DALYs-per-100,000 (ASDALYs) attributed to CLD were observed in Asia, Africa and East European regions (1,064 to 1,420), whereas the lowest ASDALYs were observed in high income regions (250 to 480). From 2007–2017, the global number of DALYs from CLD increased from 54.8 million to 62.6 million. This change represented an increase of 21.4% (17.3%–27.5%) for LC and 9.8% (4.5%–15.2%) for cirrhosis. Although HBV and HCV accounted for most DALYs in 2017 (21.8 million and 15.3 million; respectively), NAFLD showed the largest increase in DALYs from 2007 to 2017 (Figure). In fact, the highest increase in ASDALYs for LC due to NAFLD/NASH was seen in Australasia, Tropical Latin America, and South Asia (Figure).
Conclusion: In the last decade, disability from CLD related to viral hepatitis (ASDALYs from LC and cirrhosis) has improved, while the disability related to NAFLD/NASH remains important and growing. National, regional and global policies are needed to address the disability burden of NAFLD across the world.

AS064

Incorporating assessment of liver fibrosis into routine diabetic review in primary care: a pilot

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Background and Aims: Screening for non-alcoholic fatty liver disease (NAFLD) in primary care remains controversial, with guidelines conflicting. The risk of developing advanced liver fibrosis is increased in patients with type 2 diabetes, particularly those with alcohol use disorders. Diabetic patients also have regular blood tests

Figure. Percent Change in Age-Standardized DALY Rates for Liver Cancer and Cirrhosis from 2007 to 2017

	LC	LC Due to ALD	LC Due to HBV	LC Due to HCV	LC Due to NAFLD	Cirrhosis	Cirrhosis Due to ALD	Cirrhosis Due to HBV	Cirrhosis Due to HCV	Cirrhosis Due to NAFLD
Global	-4.52	-0.48	-8.22	-2.89	6.40	-10.58	-9.33	-14.69	-8.91	-2.04
Australasia	17.86	16.93	7.74	23.45	20.98	7.60	8.79	-1.37	8.82	15.97
Trop Latin Ame	10.13	10.66	5.60	10.12	20.18	-9.93	-10.76	-19.72	-10.43	1.93
S Asia	11.73	15.44	8.06	11.66	18.65	-5.76	0.34	-9.16	-3.57	5.09
MENA	2.72	3.02	1.79	0.48	16.98	-10.46	-9.52	-13.44	-9.50	2.06
HI N Ame	13.70	13.04	9.05	16.19	16.78	4.83	2.68	3.62	2.97	7.57
E Europe	2.28	5.95	-5.93	3.64	10.13	-13.64	-10.63	-24.87	-10.91	-4.44
C Asia	1.30	3.97	-3.68	1.91	9.70	-7.30	-3.91	-16.61	-4.30	4.90
Caribbean	3.36	5.58	0.96	2.54	8.45	-1.10	-0.43	-5.10	-0.73	4.81
S Latin Ame	0.70	4.34	-8.00	-0.38	7.97	-2.22	-0.70	-13.30	-1.66	6.55
C Latin Ame	-1.91	0.20	-8.13	-2.34	5.25	-6.44	-6.53	-14.80	-7.58	-0.59
SE Asia	-2.91	0.21	-5.48	-3.95	4.20	-15.23	-12.07	-18.16	-14.98	-8.88
E Asia	-6.31	0.32	-9.63	-1.30	3.88	-14.87	-7.68	-21.06	-9.86	0.46
W Europe	-2.43	-2.33	-6.13	-2.09	2.34	-15.16	-15.95	-18.74	-16.44	-11.17
Oceania	-1.78	-0.18	-3.16	-0.72	1.75	-5.61	-3.58	-8.17	-3.44	-1.19
A Latin Ame	-8.69	-6.02	-13.87	-4.54	1.17	-15.02	-15.35	-25.97	-14.84	-4.73
C Europe	-3.51	-0.99	-9.00	-3.12	0.98	-20.67	-19.41	-25.31	-20.80	-14.03
E Sub-Sah Africa	-7.50	-4.32	-10.49	-7.95	-3.62	-20.48	-19.20	-25.29	-19.67	-14.37
W Sub-Sah Africa	-13.88	-11.66	-17.60	-11.50	-6.81	-23.85	-26.69	-25.73	-20.90	-18.66
C Sub-Sah Africa	-19.55	-13.28	-24.67	-19.50	-14.94	-2.96	3.55	-9.82	-0.64	7.10
S Sub-Sah Africa	-28.07	-25.88	-31.53	-25.10	-23.12	-38.23	-38.15	-42.42	-36.76	-32.30
HI Asia Pac	-28.73	-29.67	-22.81	-33.24	-25.19	-14.88	-14.80	-15.24	-16.23	-11.84

Improving
Worsening

MENA: Middle East & North Africa; HBV, Hepatitis B virus; HCV, Hepatitis C virus; ALD, Alcohol-related liver disease

Figure: (abstract: AS063)

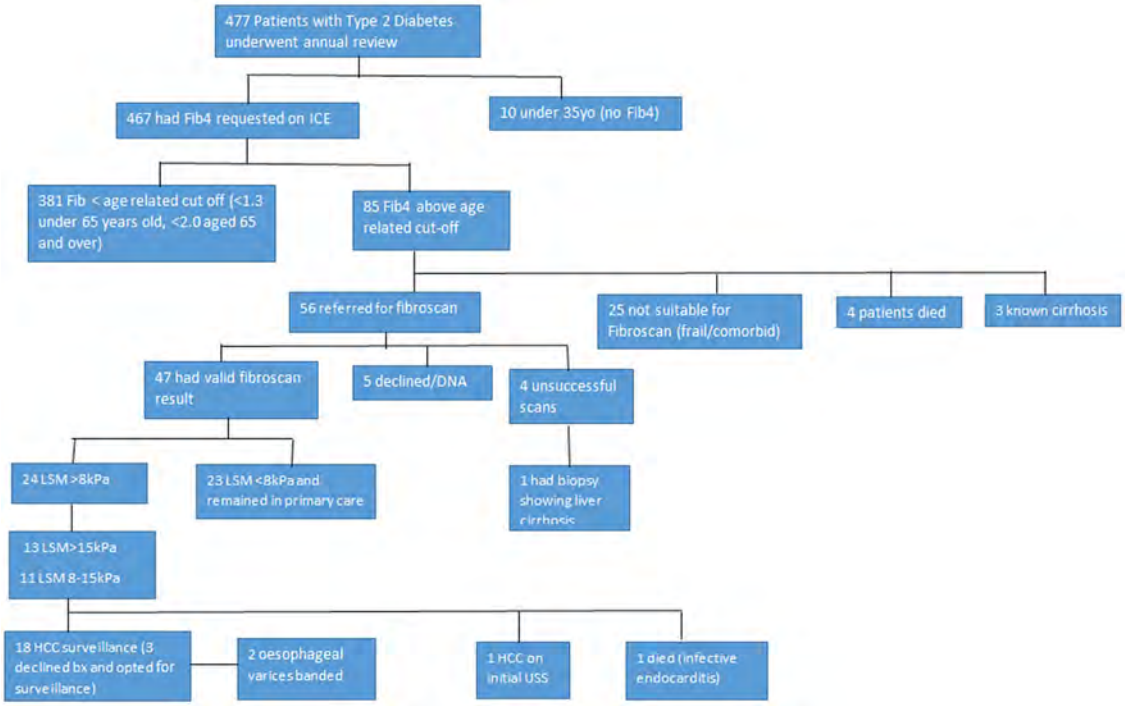

Figure: (abstract: AS064)

as part of routine review, which makes them an ideal population to screen using simple biomarkers. We present the results of a pilot incorporating two-tier assessment of liver fibrosis into routine diabetic review in primary care.

Method: 477 successive patients with Type 2 diabetes from 2 primary care practices in the North East of England underwent diabetic review April 2018–September 2019. All patients over 35 years old had a Fib4 score requested on the Electronic Medical Record (EMR) system, irrespective of alcohol intake. In patients with a Fib4 above the age related cut off, GPs were advised via EMR to request a FibroScan. Patients with a liver stiffness (LSM) of ≤8 kPa had results returned to the GP, with advice to repeat staging in 3 years' time. Patients with LSM >8 kPa were seen in secondary care. Patients thought to have advanced fibrosis/cirrhosis on specialist assessment were enrolled into surveillance programs. Where there was uncertainty, patients were offered liver biopsy. Screening for varices was performed according to Baveno VI criteria. At the end of the pilot, outcomes of patients undergoing screening were assessed.

Results: A summary of the results can be seen in the Figure. The overall rate of advanced fibrosis/cirrhosis was 4.8%, but significantly higher in patients drinking more than 14/21 units per week (31% versus 4.4% p = <0.0001). This pathway led to a 500% increase in the diagnosis of advanced liver disease/cirrhosis. 50% of patients with significant fibrosis (LSM >8 kPa) and 53.8% of patients with "advanced liver disease" (LSM >15 kPa) had "normal" ALT, and so would have been missed by following national guidelines.

Conclusion: To our knowledge, this is the first pathway incorporating two-tier liver fibrosis assessment into routine diabetic reviews in primary care. We identified a significant number of patients with advanced liver disease, over half of whom had normal ALT. Making Fib4/FibroScan accessible through EMR in primary care allows liver fibrosis assessments to be embedded into routine assessment of diabetic patients, and ensures the correct patients are referred to secondary care.

AS065

The effect of maternal pre-pregnancy obesity and infant nutrition on the development of non-alcoholic fatty liver disease in young adults - experience from the Avon longitudinal study of parents and children

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Background and Aims: The importance of the maternal-infant dyad in the genesis of nonalcoholic fatty liver disease (NAFLD) is of increasing interest. The Avon Longitudinal Study of Parents and Children (ALSPAC) has prospectively phenotyped its participants over the last 28 years. Other studies have found a protective effect of longer breastfeeding duration and normal pre-pregnancy body mass index (BMI) on development of NAFLD in young people. ALSPAC identified a NAFLD prevalence of over 20% by transient elastography (TE) and controlled attenuated parameter (CAP) amongst its participants as young adults (mean age 24 years). We test the association between maternal pre-pregnancy BMI and breastfeeding duration on offspring developing NAFLD in young adulthood using ALSPAC.

Method: 4021 participants attended clinic for TE and CAP results using the Echosens 502 Touch®. Participants with excessive alcohol consumption were excluded from analysis. Exposures of interest were

exclusive and non-exclusive breastfeeding duration of ≥ 6 months and maternal pre-pregnancy BMI. Our outcome was NAFLD at 24years. Multivariable regression models tested the association between the exposures and outcome adjusted for maternal age at parturition, smoking during pregnancy, birthweight and socio-economic status (SES). We also assessed participants' waist circumference at 24 years as a surrogate adiposity marker. Statistical analysis was performed using Stata MP 15.1.

Results: Mean age was 24 years (SD 0.8). 3128 participants had valid CAP results of whom 680 participants (20.8%) had steatosis; 331 (10.1%) had S3 steatosis (≥ 66% steatosis). 2539 participants had maternal characteristics available. A pre-pregnancy obese BMI was associated with steatosis in offspring following adjustment for covariates (OR 3.18 [95% CI 2.13–4.74]; p < 0.001). Exclusive breastfeeding for >6 months was associated with an 11% reduction in steatosis in offspring, with the CI including the null after adjustment for covariates (OR 0.89 [0.63–1.27]; p = 0.71). Similarly, non-exclusive breastfeeding duration had a protective effect on steatosis in offspring, but the CI again included the null after adjustment of the same covariates (OR 0.92 [0.67–1.26]; p = 0.71). An increased waist circumference was positively associated with steatosis presence following adjustment for covariates (OR 10.08 [7.73–13.16]; p < 0.001).

Conclusion: This is one of the largest studies to explore the relationship of breastfeeding duration and maternal pre-pregnancy BMI on NAFLD outcomes in young adulthood. Maternal pre-pregnancy BMI is strongly associated with development of NAFLD in offspring with the relationship appearing to persist into young adulthood. Further emphasis on addressing the obesogenic environment contributing to obesity in women of child-bearing age in the UK is required to mitigate development of NAFLD in their offspring.

AS066

Association of metabolic risk factors with risk of cancer and all-cause mortality in patients with chronic hepatitis B virus infection: a Korean nationwide cohort study

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Background and Aims: Long-term antiviral therapy can effectively suppress viral replication and improve clinical outcomes, but it cannot eliminate the risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B. This study aimed to elucidate the association of metabolic risk factors with the risk of developing HCC, non-HCC cancer, and all-cause mortality.

Method: This nationwide population-based study from the Korean National Health Insurance Service database consisted of adults with chronic hepatitis B virus (HBV) infection who underwent health examinations from 2007 through 2012. We collected baseline data of the study patients on metabolic risk factors, including obesity, hypercholesterolemia, insulin resistance, and hypertension. The risks of developing HCC, non-HCC cancer, and death from any cause were analyzed according to metabolic risk profile. Patients were followed up until the date of cancer diagnosis, death, or December 31, 2017. The risk of HCC and non-HCC cancer were analyzed after adjusting death as a competing risk event.

Results: The study population comprised of 317,856 patients (median age, 46 years [interquartile range, 37–54 years], 219,418 men [69.0%]) had 2,609,523.8 person-years of follow-up. During a median follow-up period of 8.5 years, 18,850 HCCs, 22,164 non-HCC cancers, and 15,768 deaths were observed. The cumulative incidences of HCC (p < 0.0001; panel A), non-HCC cancer (p < 0.0001; panel B), and death (p < 0.0001; panel C) rose with increasing number of metabolic factors. The number of metabolic factors were positively associated with the risks of HCC (p < 0.0001 for trend), non-HCC cancer (p < 0.0001 for trend), and all-cause mortality (p < 0.0001 for trend). In patients with 3 or more metabolic risk factors, the adjusted hazard ratios for HCC, non-HCC cancer, and all-cause mortality were 1.23 (95% confidence interval [CI], 1.16–1.31), 1.34 (95% CI, 1.27–1.41), and 1.31 (95% CI, 1.23–1.39), respectively, compared to those with the lowest metabolic risk profile. Among patients who received antiviral treatment for over 5 years, the risks of HCC (n = 34,725; p < 0.0001), non-HCC cancer (n = 36,809; p < 0.0001), and mortality (n = 39,061; p < 0.0001) increased substantially as the sum of metabolic risk factors increased.

Conclusion: In this Korean nationwide cohort study, the burden of metabolic risk factors was associated with increased risk of HCC, non-HCC cancer, and all-cause mortality in patients with chronic HBV infection.

Hepatitis B and D – Drug Development

AS067

Hepatitis B virus (HBV) surface antigen (HBsAg) inhibition with isis 505358 in chronic hepatitis B (CHB) patients on stable nucleos (t)ide analogue (NA) regimen and in NA -naive CHB patients: phase 2a, randomized, double-blind, placebo-controlled study

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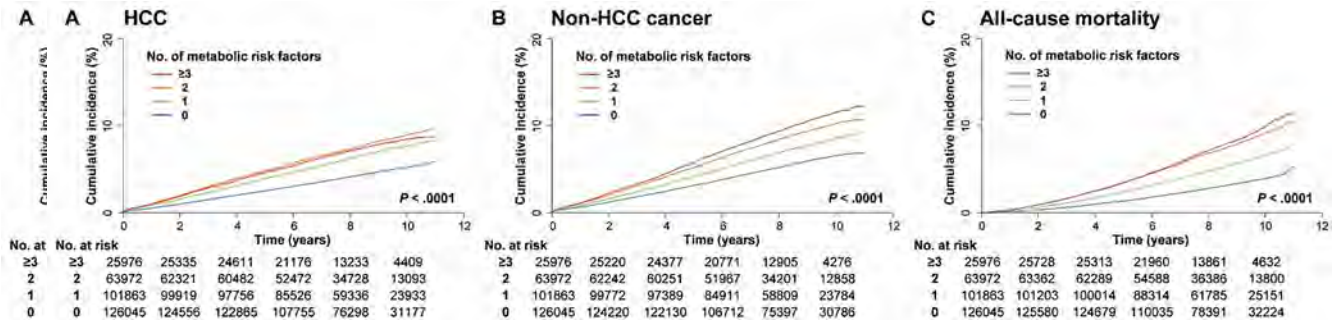
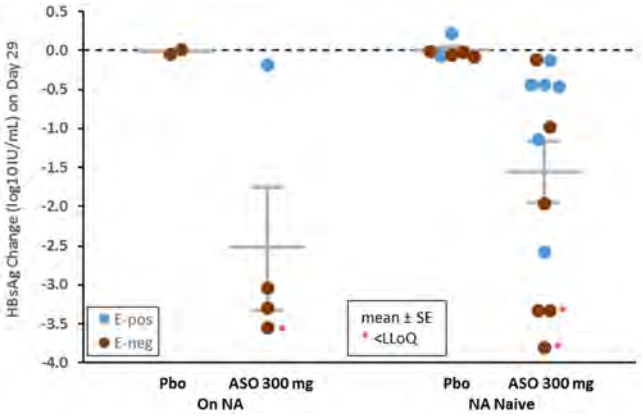


Figure: (abstract: AS066)

Background and Aims: HBsAg plays a major role in enabling and maintaining persistent HBV infection by repressing host immune responses against the virus. ISIS 505358 (now known as GSK3228836) is a 2´-MOE modified antisense oligonucleotide (ASO) targeting all HBV RNAs. The aim of the current study was to evaluate antiviral activity and safety in CHB patients.
Method: All patients were HBsAg positive ≥ 6 month and were >50 IU/mL at screening. Patients on NA were on stable regimen ≥ 12 months with plasma HBV DNA below lower limit of quantitation (LLoQ, 20 IU/mL). NA-naïve patients had HBV DNA ≥ 2×10^3 IU/mL. Exclusion criteria included: liver cirrhosis; HCV, HIV, or HDV coinfection; ALT or AST >5xULN, or bilirubin >1.1xULN. Both HBeAg positive and negative patients were eligible. ASO (300 mg) or placebo was administered subcutaneously on Days 1, 4, 8, 11, 15, and 22. The primary assessment for effect on HBV was on Day 29.



Results: For patients on NA, mean HBsAg log10 IU/mL ±SE change from baseline was −2.514 ± 0.783 for ASO (n = 4) and −0.008 for placebo (Pbo, n = 2). In ASO group, 3 patients had reductions >3.0 log10 IU/mL where one was <LLoQ (0.05 IU/mL). Another reached <LLoQ on Day 36. For NA-naïve patients, HBsAg mean changes for ASO (n = 12) were −1.556 ± 0.398 (p = 0.001 vs Pbo, n = 6) and was −1.655 ± 0.427 (p < 0 001) for HBV DNA. Three and 4 ASO patients had HBsAg and HBV DNA reductions >3.0 log10 IU/mL, respectively, where 2 and 1 also had levels reduced to <LLoQ. One SAE occurred in the study: post-ASO treatment ALT flare to 781 U/L (24xULN) in a patient with HBsAg and HBV DNA reductions to <LLoQ. Post-ASO ALT flares with peaks ranging from 1.7 to 15xULN occurred in the other HBsAg<LLoQ patients. ALT flares were asymptomatic and self-resolved. The most common adverse events for the 300 mg ASO patients (5 of 17) were at injection sites [erythema, pain, pruritus, swelling, and/or bruising].
Conclusion: Significant reductions of HBsAg levels were observed with 4-week ISIS 505358/GSK3228836 treatment in both patients on stable NA regimens and NA-naïve patients. Significant reductions in HBV DNA were also observed in naïve patients. The tolerability and safety were acceptable for proceeding to longer treatment durations.
This study was financially supported by GlaxoSmithKline.

AS068

Preliminary safety and antiviral activity of VIR-2218, an X-targeting HBV RNAi therapeutic, in chronic hepatitis B patients

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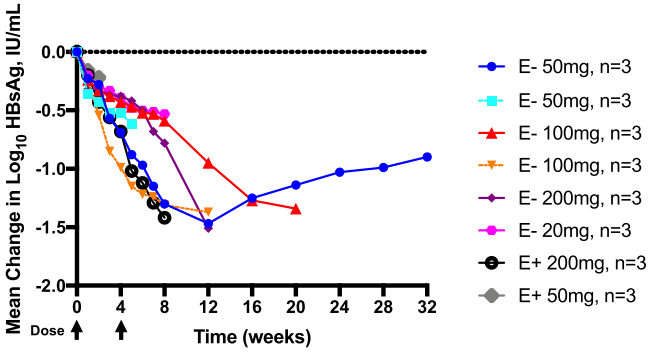
Background and Aims: VIR-2218 is an investigational GalNAc-conjugated ribonucleic acid interference (RNAi) therapeutic in development for functional cure of chronic hepatitis B virus infection (CHB). VIR-2218 was created using Enhanced Stabilization Chemistry Plus (ESC+), which retains enhanced metabolic stability needed for in vivo potency while reducing sequence matched off-target effects. VIR-2218 is designed to silence all HBV transcripts, from both cccDNA and integrated DNA, across all 10 HBV genotypes. We present interim safety and antiviral activity data from a Phase 2 trial of VIR-2218 in patients with CHB.
Method: HBeAg- or HBeAg+, virally suppressed patients on nucleos(t)ide reverse transcriptase inhibitor therapy and without significant fibrosis/cirrhosis received 2 subcutaneous doses of VIR-2218 or placebo on Day 1 (Week 0) and Day 29 (Week 4). Four cohorts of HBeAg- subjects received 20, 50, 100 or 200 mg; two cohorts were added at the 50 and 100 mg dose levels. Two cohorts of HBeAg+ subjects received 50 or 200 mg. Each cohort includes 4 subjects randomized 3:1 to receive VIR-2218 or placebo. Assessments included safety and HBsAg levels with 12 week follow-up after the second dose for all patients and an additional 32 weeks follow-up for patients achieving a pre-specified HBsAg decline target.



Results: In this ongoing trial, 24 patients with CHB have received VIR-2218 and are at varying stages of follow-up. No patients discontinued due to an adverse event (AE) and the majority of treatment emergent AEs were mild in severity. No clinically significant ALT elevations were observed. A subset of patients in the 50 mg dose level have achieved maximal decline in HBsAg levels at Week 12, with a mean decline of 1.5 $\log_{10}$ from baseline in VIR-2218 treated patients (see Figure). Notably, a mean decline of 1.0 $\log_{10}$ in HBsAg has been maintained through Week 28 in this cohort. Declines in HBsAg continue in other cohorts with at least two patterns observed: an early response and a delayed response. Data through at least Week 16 will be presented for all dose levels.

Conclusion: Two monthly doses of VIR-2218 at 20–200 mg were well tolerated in CHB patients. Substantial reductions in HBsAg were observed in both HBeAg- and HBeAg+ patients and across all dose levels. Differential patterns of decline suggest that early responses (<8 weeks) in HBsAg may not predict the final magnitude of decline. Evaluation of VIR-2218 in CHB patients is ongoing.

AS069

RO7062931 antisense oligonucleotide phase 1 study demonstrates target engagement in patients with chronic hepatitis B on established nucleos(t)ide therapy

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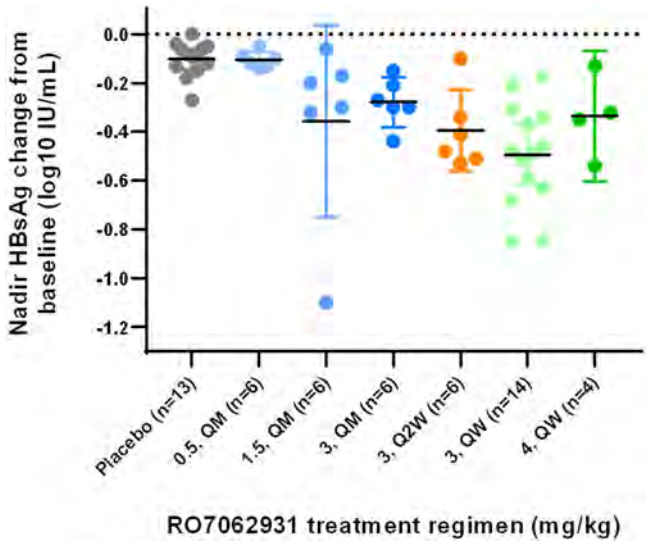
Background and Aims: RO7062931 is a N-acetylgalactosamine (GalNAc) conjugated single-stranded oligonucleotide (SSO) with locked nucleic acid (LNA) that results in RNAse H mediated degradation of HBV transcripts. We previously reported (AASLD 2019) results from Part 1 of the Phase 1 study (NCT03505190) where single doses of RO7062931 up to 4 mg/kg were safe and well tolerated in healthy volunteers (HVs). Herein we present the results from Study Part 2 of multiple dose RO7062931 treatment regimens in patients with chronic hepatitis B (CHB).

Method: 59 CHB patients on established nucleos(t)ide therapy were randomized 3:1 to RO7062931 (0.5, 1.5, 3, or 4 mg/kg) or placebo across six 4-week treatment regimens. Eligible subjects were HBeAg-positive or negative at screening with serum levels of HBsAg ≥ 1,000 IU/mL, HBV DNA ≤90 IU/mL and ALT ≤1.5× upper limit of normal (ULN). Depending on the dosing frequency (monthly [QM], bi-weekly [Q2W] or weekly [QW]), subjects received between 2–5 subcutaneous RO7062931 doses in total. Subsequently, all subjects entered a 12-week post-treatment follow-up.

Results: Majority of subjects were male (88%), Asian (90%), with a mean (range) age of 45 (25 to 65) years. At baseline, 58% were HBeAg-negative, 86% had ALT ≤ULN, and the mean HBsAg level was 5,172 (952 to 27,620) IU/mL. No serious AEs, severe AEs, or withdrawals due to AEs were reported. Injection site reactions were reported for 7 (12%) subjects, of which 5 and 2 were of mild and moderate intensity, respectively. Laboratory safety parameters were unremarkable except for 2 subjects (3 mg/kg QW group) with transient ALT >3× ULN elevations that were associated with declining HBsAg levels.

RO7062931 treatment was associated with dose-dependent reductions in HBsAg. At Day 29, mean (SD) change in HBsAg IU/mL levels were –0.03 (0.05) in the placebo group; –0.03 (0.04), –0.15 (0.21) and –0.17 (0.07) in the 0.5, 1.5 and 3 mg/kg QM groups; –0.23 (0.17) and –0.38 (0.25) in the 3 mg/kg Q2W and QW groups; and –0.14 (0.28) in the 4 mg/kg QW group. Nadir HBsAg change from baseline data with mean ± 95CI are shown in below Figure, which were similar regardless of baseline HBeAg status. A rebound in HBsAg levels was typically evident by 2–3 weeks post-treatment, which returned to baseline levels by 12-weeks post-treatment. Pharmacokinetic data in CHB patients was consistent to that previously reported for HVs.



Conclusion: RO7062931 administered over 4-weeks, at doses of up to 4 mg/kg, in CHB patients is safe, well tolerated, and demonstrates target engagement by antiviral activity.

AS070

Antiviral activity and safety of the hepatitis B core inhibitor ABI-H0731 administered with a nucleos(t)ide reverse transcriptase inhibitor in patients with HBeAg-negative chronic hepatitis B infection

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Background and Aims: Nucleos(t)ide reverse transcriptase inhibitors (NrtI) are the standard of care for the treatment of chronic HBV (CHB) infection. While these agents achieve viral suppression in most patients (pts), sustained response is rarely achieved following cessation of treatment. The HBV core inhibitor ABI-H0731 (731) in combination with a NrtI is currently being evaluated in Phase 2 clinical studies.

Method: ABI-H0731-201 is a double-blind, placebo (Pbo)-controlled study in NrtI-suppressed pts with CHB. Patients were randomized 3:2 to receive 731 (300 mg QD) +NrtI or Pbo+NrtI for 24 wks. Eligible pts had HBV DNA ≤LLOQ for ≥ 6 mos, HBsAg >1000 IU/mL, ALT ≤5× ULN and Metavir F0-F2. HBV DNA was measured by COBAS TaqMan 2.0 (LLOQ = 20 IU/mL) and an in-house (ASMB) semi-quantitative PCR assay (LLOQ = 5 IU/mL). HBV pgRNA was measured by an ASMB RT-qPCR assay (LLOQ = 35 IU/mL). Safety was assessed through reporting of adverse events (AE) and laboratory abnormalities. This report summarizes the antiviral activity and safety for the HBeAg-negative pts only.

Results: Of the 26 HBeAg-negative pts enrolled in the study, 16 received 731+NrtI and 10 received Pbo+NrtI. Overall, the mean (range) age was 48 (34–64) years, 16 (62%) were male, 21 (81%) were Asian. Results are shown in the table. Treatment with 731+NrtI resulted in a higher proportion of pts achieving TND by the ASMB HBV DNA assay compared with Pbo+NrtI. At baseline and throughout the study, the pgRNA and HBcrAg levels were low and the HBsAg levels did not change. The safety profile of 731+NrtI was similar to Pbo +NrtI. Both treatments were well-tolerated, with no serious adverse events or discontinuations due to AEs. All AEs and lab abnormalities were mild or moderate in severity. Only one pt receiving 731+NrtI reported a Grade 1 rash that resolved on study without treatment interruption. No Grade 3 ALT elevations were observed.

	ABI-0731 + NrtI (N=16)		Placebo + NrtI (N=10)	
	Baseline	Week 24	Baseline	Week 24
HBV DNA (COBAS)[1], n (%)				
≥20 IU/mL	0	1 (6)	0	0
<20 IU/mL, TD	6 (38)	2 (13)	3 (30)	4 (40)
<10 IU/mL, TND	10 (63)	13 (81)	7 (70)	6 (60)
HBV DNA (ASMB)[2], n (%)				
TD	6 (38)	1 (6)	2 (20)	3 (30)
TND	10 (63)	15 (94)	8 (80)	7 (70)
HBV pgRNA (ASMB)[3], n (%)				
<LLOQ	13 (81)	15 (94)	9 (90)	10 (100)
HBcrAg, mean (SD) in Log_{10} kU/mL	0.29 (0.90)	0.23 (0.81)	0.54 (0.70)	0.38 (0.87)
HBsAg, mean (SD) in Log_{10} IU/mL	2.99 (0.56)	3.09 (0.55)	3.35 (0.65)	3.35 (0.64)
ALT, mean (SD) in U/L	27 (14)	22 (7)	21 (10)	21 (12)

[1]TaqMan 2.0; [2] LLOQ=5 IU/mL; [3] LLOQ=35 U/mL

Conclusion: In 24 weeks of treatment, a higher proportion of HBeAg-negative pts receiving 731+NrtI achieved HBV DNA TND by highly sensitive PCR methodology compared to Pbo+NrtI. 731 has a favorable safety and tolerability profile. These data suggest the contribution of 731 to the standard of care in achieving deeper viral suppression and support continued treatment with 731+NrtI in the open-label Phase 2 study ABI-H0731-211.

AS071

Efficacy and safety of 24 weeks treatment with oral TLR8 agonist, selgantolimod, in virally-suppressed adult patients with chronic hepatitis B: a phase 2 study

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Background and Aims: Selgantolimod (GS-9688, SLGN), an oral selective small molecule agonist of Toll-like receptor 8 (TLR8), in clinical development for the treatment of chronic hepatitis B. Here we present the results through Week 48 (24 weeks post-SLGN) on the safety and efficacy.

Method: Patients were randomized in 2 cohorts (HBeAg-positive and -negative) to SLGN 3 mg, 1.5 mg, and PBO (2:2:1) once a week for 24 weeks while maintaining OAV. Safety assessments included monitoring of adverse events (AE) and laboratory abnormalities. The primary efficacy endpoint was the proportion of patients with ≥ 1 log10 IU/mL decline in HBsAg levels from baseline at week 24. Secondary endpoints include the proportion of patients with HBsAg and HBeAg loss and changes in pharmacodynamic (PD) markers including cytokines (IL-1RA and IL-12p40) and immune cell subsets evaluated using spectral flow cytometry (four 23- to 26-colour panels covering myeloid, T-, B-, and NK-cell subsets).

Results: 48 patients randomized (24 HBeAg-positive and 24 -negative). Baseline characteristics were similar across groups: majority were Asian (58%), male (75%) with a mean (SD) age of 47 (9) y and HBsAg of 2.9 (1.1) log10 IU/mL. Week 48 serologic responses are shown in the table. HBsAg loss, HBeAg loss, and HBsAg decline were more apparent in SLGN arms v PBO, with 21–30% of patients in SLGN arms having HBsAg declines ≥ 0.1 log10 IU/mL at Week 48. No patients experienced virologic breakthrough in the study. There were no Grade 3 or 4 AEs in the 3 mg SLGN or PBO groups; 3 patients in the 1.5 mg arm had Grade 3 AEs, none of which led to early discontinuation. Most frequently (≥ 20% SLGN-treated) reported AEs (SLGN v PBO) were: nausea (46% v 0), URTI (23% v 33%), headache (21% v 44%), vomiting (23% v 0), and fatigue (21% v 11%). GI disorders were mostly mild and transient. Dose-proportional increases in cytokines were observed. The 4 h post-SLGN, Days 1 and 23 median (IQR) IL-12p40 for 3 mg, 1.5 mg, and PBO were 6.0 (3.9–10.4) and 6.9 (4.7–8.2), 3.0 (1.9–4.4) and 3.9 (2.9–4.9), 0.9 (0.8–1.0) and 1.0 (0.9, 1.0) pg/mL, respectively. No tachyphylaxis were observed during 24 weeks of SLGN treatment. Further immunologic characterizations of patients with serologic responses is underway.

Week 48 Results	SLGN 3mg	SLGN 1.5mg
HBsAg loss	1/19 (5%)	1/20 (5%)
HBeAg loss	2/9 (22%)	1/10 (10%)
HBsAg decline >0.1log_{10}	4/19 (21%)	6/20 (30%)

Conclusion: Oral SLGN up to 3 mg once weekly for 24 weeks is generally safe and well-tolerated. ≥ The dose-dependent PD changes and no tachyphylaxis observed during treatment support once weekly administration of SLGN. HBsAg loss were observed in 2 patients and HBeAg loss in 3 patients by follow up Week 24.

AS072

48 weeks of high dose (10 mg) bulevirtide as monotherapy or with peginterferon alfa-2a in patients with chronic HBV/HDV co-infection

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Background and Aims: Bulevirtide (BLV) is a first-in-class entry inhibitor to treat HBV/HDV co-infected patients. BLV monotherapy as well as combination with Peginterferon alfa-2a (PEG-IFNα) for 48 weeks induced serum and intrahepatic HDV RNA declines in two phase 2 trials (MYR202/203). Combination therapy with low-dose (2 mg and 5 mg) BLV and PEG-IFNα showed strong synergistic effects on HDV RNA and induced HBsAg responses (>1log decline, negativation and seroconversion) in a substantial number of patients. We here present the results of 48 weeks end of treatment of chronically HBV/HDV infected patients receiving high-dose (10 mg) BLV as monotherapy or in combination with PEG-IFNα.
Method: 30 patients with chronic HBV/HDV co-infection were randomized in 2 arms receiving: 10 mg BLV q.d./day s.c. in combination with 180 µg PEG-IFNα once weekly (E; n = 15) or 5 mg BLV b.i.d./ day s.c. (total daily dose of 10 mg BLV; F; n = 15) for 48 weeks. Tenofovir (TDF) was co-administered in F to control the underlying HBV infection. Patients were followed for 24 weeks: treatment-free follow-up (E) and continuous TDF treatment (F). The primary endpoint was defined as undetectable HDV RNA (LOD <10 IU/ml) at week 72 (24 weeks off therapy); secondary endpoints included ALT normalization, combined treatment response (≥ 2log serum HDV RNA decline + normal ALT levels), and HBsAg response.
Results: *Safety:* BLV was well tolerated during 48 weeks of therapy: overall 487 AEs were reported of which 143 AEs were considered related to BLV with most frequent AE being asymptomatic bile salt increase. No SAE was reported. *Efficacy:* At week 48, serum HDV RNA levels declined in both arms with median reductions from baseline by −6.09 $\log_{10}$ IU/ml (E) and −4.58 $\log_{10}$ IU/ml (F). HDV RNA was undetectable in 86.7% and 40% of patients at week 48, respectively. Mean ALT levels progressively declined during treatment in both groups, with 26.7% and 40% ALT normalization at week 48 in E and F, respectively. HBsAg became undetectable in one patient treated with BLV/PEG-IFNα.
Conclusion: High-dose administration of BLV co-administered with PEG-IFNα or TDF for 48 weeks was safe and well tolerated. Continuous linear HDV RNA decline was maintained over 48 weeks of treatment in monotherapy group. Strong synergy against HDV was confirmed using 10 mg BLV in combination with PEG-IFNα. 24-week follow-up data will be presented during the meeting.

NAFLD – Pharmacological therapy

AS073

VK2809, a novel liver-directed thyroid receptor agonist, produces durable reductions in liver fat in patients with non-alcoholic fatty liver disease: results of 4-week follow-up assessment from a 12-week phase 2 randomized, placebo-controlled trial

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Background and Aims: Thyroid hormone is an important regulator of lipid metabolism, particularly acting via the beta isoform of the hepatic T3 receptor. VK2809 is a small molecule prodrug of a potent thyroid receptor agonist. VK2809 is selectively cleaved in hepatic tissues by the action of cytochrome P450 isozyme 3A4, to release a pharmacologically active metabolite. A 12-week study in patients with non-alcoholic fatty-liver disease (NAFLD) and hypercholesteremia demonstrated robust liver fat reductions and encouraging safety and tolerability. We report herein the results of liver fat assessments taken at 16 weeks; 4-weeks post-completion of dosing.
Method: This was a multi-center, randomized, double-blind, placebo-controlled, Phase 2 trial. Patients having liver fat content ≥ 8% as assessed by magnetic-resonance-imaging, proton-density-fat-fraction (MRI-PDFF), LDL-C ≥ 110 mg/dL and triglycerides ≥ 120 mg/dL were randomized to receive either oral VK2809 doses of 5 mg QD, 10 mg QOD, 10 mg QD, or placebo for 12 weeks. Patients returned for MRI-PDFF and safety assessments at 16 weeks, 4 weeks following completion of dosing.
Results: Patients receiving VK2809 experienced statistically significant reductions in liver fat content by MRI-PDFF, relative to placebo following 12 weeks of treatment. These effects were maintained at the Week-16 assessment, with patients continuing to demonstrate significantly reduced liver fat relative to baseline and placebo. At Week 16, mean relative change from baseline in liver fat content was 53% for VK2809 5 mg QD ($p < 0.0001$), 42% for VK2809 10 mg QOD ($p = 0.0004$), and 34% for 10 mg QD ($p = 0.0018$), vs 18% for placebo. Among all patients receiving VK2809 therapy, 70% maintained a ≥ 30% reduction in MRI-PDFF at Week 16 vs. 22% for placebo ($p = 0.0083$). The proportion of VK2809 patients maintaining ≥ 5% absolute liver fat reduction was 56%, vs. 0% for placebo ($p = 0.013$). VK2809 was well-tolerated in this study; no serious adverse events were reported in any cohort.
Conclusion: These data are the first to show that treatment of NAFLD patients with the novel oral thyroid receptor-beta agonist VK2809 for 12 weeks produces a durable improvement in liver fat content. Significant reductions in MRI-PDFF are maintained 4 weeks following completion of dosing. These results provide strong rationale for further development of VK2809 and may indicate opportunities for intermittent dosing regimens or potential cycling of treatment modalities in the setting of NAFLD or NASH.

AS074

Novel first-in-class, fatty acid synthase inhibitor, TVB-2640 vs. placebo demonstrates clinically significant reduction in liver fat by MRI-PDFF in NASH: a phase 2 randomised controlled trial (FASCINATE-1)

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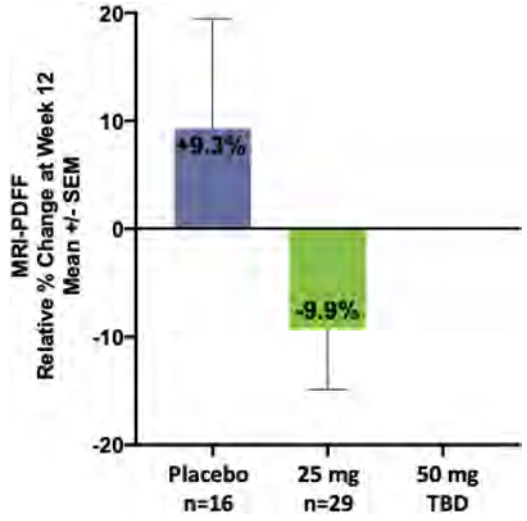
Background and Aims: TVB-2640 is an oral, first-in-class, small molecule reversible FASN inhibitor. FASN mediates the last committed step in de novo lipogenesis (DNL) which converts dietary sugar into palmitate. Increased hepatic DNL increases liver fat content and has been linked to lipotoxicity, a hallmark for non-alcoholic steatohepatitis. This Phase 2 study assessed the efficacy and safety of TVB-2640 in NASH (NCT03938246).
Method: Patients with NASH were randomized to either placebo or TVB-2640 at 25 mg or 50 mg QD in sequential cohorts, for 12 weeks. The primary endpoints were changes in liver fat content by Magnetic

Resonance Imaging Proton Density Fat Fraction (MRI-PDFF) and percentage of patients with at least a 30% reduction in liver fat at Week 12. Secondary and additional endpoints include the effect on safety evaluations, serum ALT and AST, cholesterol, triglycerides, lipoproteins, eicosanoids and liver fibrosis markers.

Results: The 25 mg versus placebo cohort has been completed (n = 45). The patients were predominantly Hispanic and 75% had type 2 diabetes. Twelve weeks of treatment with 25 mg TVB-2640 (n = 29) decreased liver fat by MRI-PDFF with a mean relative difference of 19.2% compared to placebo (n = 16). Seven of 29 patients treated with TVB-2640 achieved a ≥ 30% relative decrease (MRI-PDFF responders). The MRI-PDFF responders also had a statistically significant 34.6% reduction in mean serum ALT compared to a 9.3% increase in MRI-PDFF non-responders (p = 0.005). Serum fibrosis (TIMP1, PIIINP) and inflammation (IP-10) biomarkers were significantly decreased in responders versus non-responders. A significant trend was demonstrated between reductions in plasma tripalmitin and reductions in liver fat. Eicosanoid analysis is ongoing. No serious adverse events were observed and adverse events were primarily grade 1 (mild). Compared to placebo there was no significant difference in triglycerides and no hematologic or serum chemistry toxicities. The 50 mg dose cohort (30 active, 15 placebo) is ongoing and TVB-2640 continues to be well tolerated.



Conclusion: In this proof-of-concept randomized controlled trial, a novel, first in class, FASN inhibitor, TVB-2640, has shown clinically significant decreases in liver fat and serum biomarkers of liver injury, fibrosis and inflammation with impressive safety and tolerability. FASN inhibition is a promising therapeutic approach in patients with NASH and further investigation of TVB-2640 is underway.

AS075

Obeticholic acid improves experimental non-invasive markers of non-alcoholic steatohepatitis and advanced fibrosis: a secondary analysis of the phase 3 regenerate study

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Background and Aims: The REGENERATE month-18 interim analysis showed that treatment with OCA improved liver fibrosis in patients with NASH[1] as well as established non-invasive assessments of fibrosis and NASH. New biomarker indices are being developed to improve ability to predict NASH grade and fibrosis stage. FibroMeter (FM) is designed to predict presence of significant fibrosis (F ≥ 2). FM combines age, gender, alpha 2 macroglobilin (A2M), INR, platelets, urea and GGT, while FM VCTE uses the same biomarkers except urea and includes liver stiffness (LS) by vibration-controlled transient elastography (VCTE). The FAST score, designed to identify patients with NASH and NAFLD Activity Score (NAS) ≥ 4 and F ≥ 2, combines LS by VCTE with Controlled Attenuation Parameter (CAP) score and AST.

Method: NASH patients with fibrosis stages 2 and 3 were randomized (1:1:1) to placebo (N = 311), OCA 10 mg (n = 312) or OCA 25 mg (N = 308) QD. In a subset of patients with available values, changes in FM (N = 604), FM VCTE (N = 604), and FAST (N = 391) were analyzed using mixed-effect repeated measures model with treatment, baseline, visit, visit by treatment interaction and stratification factors to be included in the model. LS mean and p-values are based on mixed-effect repeated measure model.

Results: At baseline, there was no significant difference in scores across treatment groups (Figure). Patients with stage 3 fibrosis at baseline had higher scores than those with stage 2 fibrosis, consistent with prior publications (data not shown).

OCA-treated patients experienced improvements in FM, FM VCTE and FAST as of the first assessed timepoint (month 6) which were sustained through month 18. While this therapeutic response was observed in both OCA dose groups, no improvement was observed in the placebo group (Figure).

Conclusion: OCA treatment resulted in early and sustained improvements in experimental non-invasive assessments of fibrosis NASH, consistent with previously reported histologic improvements. Specifically, improvements in FM and FM VCTE are consistent with OCA's anti-fibrotic effect, while improvements in FAST are consistent with amelioration of key histologic features of NASH, including both inflammation and fibrosis.

AS076

Effects of cotadutide on biomarkers of non-alcoholic steatohepatitis in overweight or obese subjects with type 2 diabetes mellitus: a 54-week analysis of a randomized phase 2b study

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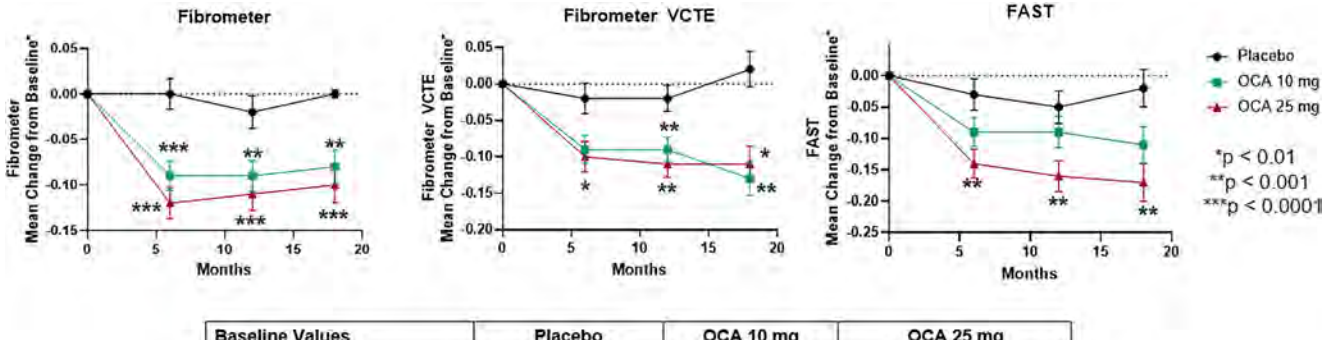
Background and Aims: Cotadutide, a dual-receptor agonist with glucagon-like peptide-1 and glucagon activity, significantly decreased hepatic fat in obese or overweight T2DM subjects in an exploratory analysis of a phase 2b study. We evaluated effects of cotadutide at week 54 (W54) on hepatic parameters and metabolic profiles of obese or overweight T2DM subjects.

[1]Interim analysis results at 18 months are based on surrogate endpoints and impact on clinical outcomes has not been confirmed. The REGENERATE study remains ongoing and will continue through clinical outcomes to characterize OCA's clinical benefit.



Baseline Values	Placebo	OCA 10 mg	OCA 25 mg
Fibrometer	0.53 (0.023)	0.57 (0.020)	0.57 (0.021)
Fibrometer VCTE	0.59 (0.025)	0.64 (0.021)	0.60 (0.024)
FAST	0.60 (0.021)	0.60 (0.023)	0.6 (0.021)

Figure: (abstract: AS075): LS Mean Change in FM, FM VCTE and FAST.

Table (abstract: AS076): Changes from BL to W54 in ALT, AST, and GGT (per-protocol population)

	Cotadutide (μg)			Liraglutide 1.8 mg (n = 104)	Placebo (n = 93)
	100 (n = 76)	200 (n = 202)	300 (n = 189)		
ALT					
Baseline, U/L[a]	33.5 (21.6)	32.1 (18.1)	33.2 (18.7)	32.8 (18.2)	30.7 (19.2)
Week 54, %[b]	−7.5	−12.0	−14.1	−3.2	0.9
95% CI	−16.4, 1.3	−17.4, −6.6	−19.8, −8.6	−10.8, 4.3	−7.1, 9.0
vs placebo	p = 0.165	p = 0.009	p = 0.003	p = 0.461	—
vs liraglutide	p = 0.467	p = 0.063	p = 0.023	—	—
AST					
Baseline, U/L[a]	24.8 (12.3)	24.1 (13.3)	25.1 (17.4)	24.6 (11.9)	23.7 (11.5)
Week 54, %[b]	−1.8	−6.2	−9.1	0.4	5.7
95% CI	−9.8, 6.3	−11.2, 1.3	−14.3, −4.0	−6.5, 7.2	−1.7, 13.0
vs placebo	p = 0.182	p = 0.009	p = 0.001	p = 0.302	—
vs liraglutide	p = 0.695	p = 0.129	p = 0.030	—	—
GGT					
Baseline, U/L[a]	40.3 (40.9)	42.5 (32.1)	45.1 (48.8)	48.1 (49.5)	41.5 (30.1)
Week 54, %[b]	−10.5	−1.5	−12.2	−10.5	12.5
95% CI	−26.8, 5.7	−11.5, 8.4	−22.5, −1.9	−24.4, 3.3	−2.3, 27.2
vs placebo	p = 0.040	p = 0.123	p = 0.007	p = 0.026	—
vs liraglutide	p = 1.000	p = 0.300	p = 0.853	—	—

[a]Mean (SD).
[b]Least-square mean for % change from BL.

Method: Eligible subjects (N = 834) were randomized to once-daily subcutaneous cotadutide 100, 200, or 300 μg; placebo; or open-label once-daily liraglutide 1.8 mg (NCT03235050). Change from baseline (BL) to W54 in body weight was secondary endpoint; changes in ALT, AST, and gamma-glutamyl transferase (GGT) were post hoc analyses (per-protocol population). Changes from BL to W54 in fatty liver disease fibrosis score (NFS) and fatty liver index (FLI) were also assessed as post hoc analyses (as-treated population).

Results: Significant reductions in body weight were observed at all cotadutide doses vs placebo ($p < 0.001$) and cotadutide 300 μg vs liraglutide ($p = 0.009$). Numerical reductions from BL to W54 in ALT, AST, and GGT levels were observed with all cotadutide doses (Table). Greatest ALT reductions were in 4th quartile (LS mean difference for % change from BL) vs placebo; with cotadutide 100, 200, and 300 μg, −12.3 ($p = 0.259$), −27.1 ($p = 0.002$), and −31.3 ($p < 0.001$), respectively. At BL, 91% had fatty liver (FLI ≥ 60) and 13% had advanced liver fibrosis (NFS >0.675). Clinically significant reductions were observed at W54 in NFS ($p \leq 0.001$) for all cotadutide doses and in FLI ($p = 0.010$) for cotadutide 300 μg vs placebo.

Conclusion: Cotadutide 300 μg yielded greater reductions in body weight and ALT levels vs liraglutide. The improvements in FLI and NFS with cotadutide may indicate reduced liver fat and fibrosis, respectively. These data support prospective clinical trials with cotadutide for a NASH indication.

AS077

Magnetic resonance imaging-proton density fat fraction (MRI-PDFF) to predict treatment response on NASH liver biopsy: a secondary analysis of the resmetirom randomized placebo-controlled phase 2 clinical trial

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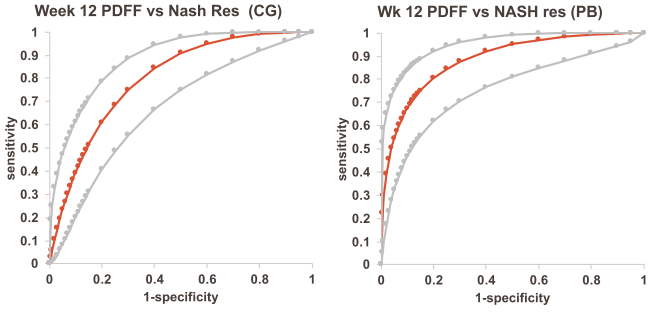
Background and Aims: Resmetirom treatment resulted in significant reduction in hepatic fat as assessed by MRI-PDFF after 12 and 36 weeks that was associated with higher rates of NASH resolution compared to placebo on week 36 liver biopsy assessment. A few placebo patients who lost body weight also demonstrated MRI-PDFF reduction and NASH resolution. The aim of this secondary analysis was to examine the potential of reduction in MRI-PDFF to predict histologic response in NASH.

Method: The analysis included the subset of patients (n = 107; placebo, n = 34; resmetirom, n = 73) who had MRI-PDFF at baseline, week 12, week 36 and week 36 liver biopsy in the Phase 2 randomized controlled trial of resmetirom versus placebo (pbo) for treatment of NASH. We examined the overall relationship in resmetirom plus pbo patients between PDFF and NASH resolution as evaluated by two blinded, independent central biopsy reviewers (CG, PB). The study cohort was assessed for those who had a ≥ 30, ≥ 40 and ≥ 50% decline in MRI-PDFF between week 0 and week 12 as predictors of NASH resolution.



Results: Baseline characteristics have been reported (Lancet https://doi.org/10.1016/S0140-6736(19)32517-6). Among pbo (n = 5,4 (CG, PB)) (3/5 pbo patients with ≥ 10% weight loss) and resmetirom (n = 18) patients with NASH resolution, the mean week 12 fat reduction on MRI-PDFF was 56%, the optimal PDFF cutoff was 41.5% with a sensitivity of 0.82 (95% confidence interval (CI) 0.61,0.93) and specificity of 0.83 (95% CI 0.74,0.90), p < 0.001, observed by both central readers (Figure). Compared to MRI-PDFF non-responders with <30% fat reduction (n = 56), MRI-PDFF responders (≥ 30% fat reduction) (n = 51) had significantly higher odds of NASH resolution (40% versus 3.7%) with odds ratio 9.1,18.0 (CG, PB) (95% CI 3.9, 82.3), p < 0.0001. The odds of NASH resolution were higher with greater reductions in liver fat content, ≥ 40% and ≥ 50% MRI-PDFF reduction showing an OR of 16.5, and 25.3, respectively, compared to PDFF non-responders, p < 0.0001. In patients with ≥ 50% fat reduction at week 12 (pbo = 2; resmetirom = 22) 46% (CG) and 64% (PB) had NASH resolution with a component response driven primarily by ballooning and inflammation reduction. Change in ALT was not strongly associated with a histologic response.

Conclusion: MRI-PDFF response robustly predicted NASH biopsy response for resmetirom and pbo. Doses of resmetirom, 80 mg and 100 mg, used in the ongoing Phase 3 study MAESTRO-NASH had average PDFF reduction of 50% and 64%, respectively, and may predict higher rates of NASH resolution than observed in the Phase 2 study (27%) in which half of the resmetirom treated patients received a lower dose (60 mg).

AS078

EDP-305, a non-bile acid farnesoid X receptor (FXR) agonist, showed statistically significant improvements in liver biochemistry and hepatic steatosis in the phase 2a argon-1 study

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Background and Aims: EDP-305 is a novel oral FXR agonist developed for the treatment of nonalcoholic steatohepatitis (NASH).

Table: (abstract: AS078)

Parameter (unit) Change from Baseline at W12	EDP-305 2.5 mg (n = 53)	EDP-305 1 mg (n = 55)	Placebo (N = 24)	P-value (2.5 mg vs. pbo)	P-value (1 mg vs. pbo)
ALT (U/L)	−27.9 (3.7)	−21.7 (3.3)	−15.4 (5.1)	**0.0495**	0.3039
MRI-PDFF (%)-absolute	−7.1 (0.7)	−3.3 (0.7)	−2.4 (1.2)	**0.0009**	0.4946
MRI-PDFF (%)-relative	−30.5 (3.6)	−15.3 (3.5)	−11.9 (5.6)	**0.0065**	0.6097
ALP (U/L)	41.8 (4.9)	16.7 (4.4)	−2.5 (6.8)	**<0.0001**	**0.0208**
GGT (U/L)	−49.4 (4)	−35.8 (3.5)	−7.7 (5.5)	**<0.0001**	**<0.0001**
C4 (ng/ml) (%)	−72%	−42%	17%	**<0.001**	**<0.001**
FGF −19 (pg/ml) (%)	574%	64%	73%	0.192	0.979
LDL (mmol/L)	0.17 (0.1)	0.12 (0.1)	−0.13 (0.14)	0.0897	0.1411
HDL (mmol/L)	−0.21 (0.03)	−0.05 (0.03)	−0.004 (0.04)	**<0.0001**	0.348

Data represents LS mean (SE) for change (or %change) from baseline at week 12.

Here, we present the final results at week 12 (W12) of a randomized, double-blind, placebo-controlled trial (NCT03421431).

Method: Non-cirrhotic subjects with fibrotic NASH diagnosed by historical biopsy or phenotypically (high BMI, diagnosis of T2DM/prediabetes), and with elevated ALT and MRI-PDFF >8%, were randomized to receive EDP-305 2.5 mg or 1 mg, or placebo (PBO), for 12 weeks. Liver enzymes and liver fat measured by MRI-PDFF were assessed at baseline (BL) and through W12.

Results: A total of 134 subjects were randomized. Mean age was 52 years; 52% were women; 74% had T2DM; mean ALT was 83U/l and MRI-PDFF, 20%. At W12, pre-specified endpoints were met in EDP-305 2.5 mg (Table). Overall, EDP-305 was generally safe, with the most common ($\geq$ 5%) TEAEs including pruritus, gastro-intestinal symptoms (nausea, vomiting, diarrhea), headache and dizziness. Pruritus was present in 51% of the subjects in 2.5 mg arm, <10% in 1 mg arm, <5% in PBO. Pruritus led to treatment discontinuation in 1.8% with 1 mg and 20.8% with 2.5 mg (due to moderate pruritus). Effects of EDP-305 on lipids were modest.

Conclusion: After 12-weeks of therapy, EDP-305 2.5 mg achieved statistically significant improvements in liver biochemistry and hepatic steatosis. EDP-305 exhibited strong target engagement with reduction in C4 and increase in FGF-19. EDP-305 was generally safe; mild to moderate pruritus was more frequent with 2.5 mg, with more treatment discontinuations. No statistical difference in LDL was observed. These results support further development of EDP-305 in patients with NASH in a longer-term trial with liver histology assessment.

EASL JOURNAL OF HEPATOLOGY

Alcohol associated liver disease

AS079

Lipidomics profiling reveals a distinct pattern of selective lipid depletion in the circulation and liver tissue in patients with progressive alcohol-associated liver fibrosis: a biopsy-controlled study in 400 people

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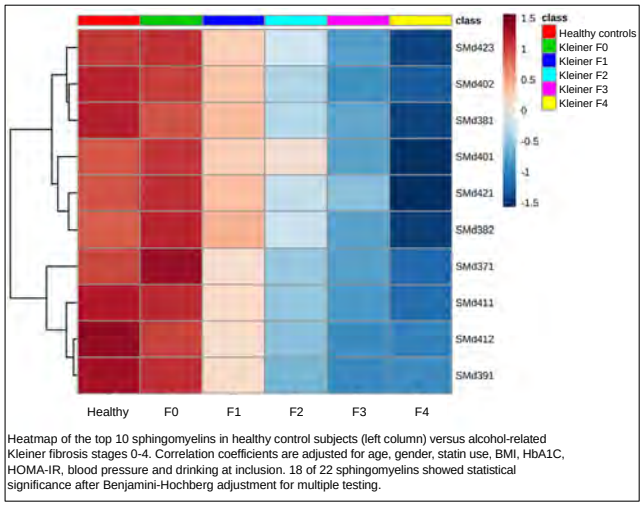
Background and Aims: Alcohol-related liver fibrosis (ALD) is the leading cause of cirrhosis and liver-related deaths. Identification of disease drivers is pivotal to better understand individual susceptibility and identify potential treatment targets. Studies in histology and genetics point towards lipid metabolism as a key feature. Advances in mass spectrometry today allow detailed analysis of individual lipids in liver tissue and in the circulation. Consequently, we aimed to fully characterize circulating and liver lipids in ALD by lipidomics analysis.

Method: We included 350 asymptomatic ALD patients and 50 healthy control subjects matched for age, gender and BMI. Plasma and liver were sampled on the same day and histology scored according to the NAFLD activity score and Kleiner fibrosis stage. We did ultra high-performance chromatography coupled with time-of-flight mass spectrometry to identify 250 lipids from 17 lipid classes, including sphingomyelins (SM), ceramides (Cer), lysophosphatidylcholines (LPC), phosphatidylcholines (PC), and triglycerides (TG). We correlated lipids with histology by adjusted ANCOVA regression, with p-value correction for multiplicity. We combined lipidomics with data from the whole-blood transcriptome and proteome to evaluate potential mechanistic effects.

Results: Sphingomyelins decreased dramatically both in circulation and liver through every fibrosis stage and were lowest in cirrhosis (Figure). We observed a similar, early decrease in SM with inflammation and steatosis. Cer, LPC, PC, and TG also correlated negatively with severe fibrosis and cirrhosis. The circulating lipidomics signature of healthy controls were comparable only to ALD patients with no fibrosis (F0). The negative correlation between SM and fibrosis stage was independent of age, gender, statin use, BMI, HbA1C, HOMA-IR, liver steatosis and drinking pattern. Circulating mRNA for enzymes in the SM biosynthesis and degradation pathways were dysregulated, but without clear evidence of either decreased formation of SM or increased degradation. Plasma proteome analysis revealed a downregulation of several apolipoproteins, suggesting hepatic and extra-hepatic decreased lipid-binding and -transporting capacity.



Heatmap of the top 10 sphingomyelins in healthy control subjects (left column) versus alcohol-related Kleiner fibrosis stages 0-4. Correlation coefficients are adjusted for age, gender, statin use, BMI, HbA1C, HOMA-IR, blood pressure and drinking at inclusion. 18 of 22 sphingomyelins showed statistical significance after Benjamini-Hochberg adjustment for multiple testing.

Conclusion: Progressive fibrosis in ALD is characterized by selective lipid depletion in blood and liver tissue, with sphingomyelins showing the most dramatic decreases. Sphingomyelins are involved in cell signaling and apoptosis, which implies a mechanistic role.

AS080

Interaction between neutrophils and cholangiocytes causes cholestasis in alcoholic hepatitis

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Background and Aims: Alcoholic hepatitis (AH) is a life-threatening disease with limited treatment options. The presence of cholestasis worsens prognosis but the responsible mechanism is unknown. AH results in infiltration of polymorphonuclear neutrophils (PMNs) in the liver, and cholestasis often reflects bile duct pathology, so we investigated whether and how PMNs interact with cholangiocytes in AH.

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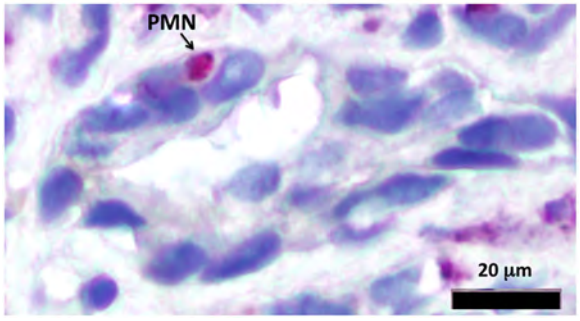
Method: PMNs in contact with bile ducts were identified (Fig.) and quantified in archived liver biopsy specimens from patients with AH, alcoholic cirrhosis, and normal controls, then these results were correlated with clinical and pathological findings. NHC cells derived from human bile ducts were co-cultured with PMNs isolated from AH patients or normal controls. Type 3 inositol trisphosphate receptor (ITPR3) expression in NHC cells was used as a marker for cholestasis because loss of this apical calcium channel is responsible for impaired secretion in AH and other, more classical cholangiopathies.

Results: PMNs were adjacent to bile ducts in most AH specimens but not in alcoholic cirrhosis or normal control specimens. The frequency of PMN-bile duct contacts correlated with serum bilirubin and alkaline phosphatase ($p < 0.0005$), and cholestasis in the hepatic lobule was only seen when PMNs were in contact with bile ducts ($p < 0.0001$). ITPR3 expression in NHC cells was markedly reduced by PMN co-culture, and PMNs from AH patients were more potent than healthy control PMNs ($p < 0.05$). This effect was not reduced by blocking components of the LPS/TLR4/NFkB pathway. ITPR3 in NHC cells also was not reduced by PMN-conditioned medium or by PMNs separated by a semi-permeable membrane, suggesting that direct contact was necessary. Consistent with this, ITPR3 expression in NHC cells was only minimally reduced by co-culture with "naked" PMNs in which surface membrane proteins were removed in a non-damaging fashion. Bioinformatic analysis of RNA-seq data suggested the involvement of β1-integrin in PMN-NHC cell interactions, and PMNs did not decrease ITPR3 expression in NHC cells in the presence of an integrin blocking antibody.



Conclusion: Neutrophils often are in contact with bile ducts in alcoholic hepatitis, and this interaction correlates with jaundice and cholestasis in these patients. This is an integrin β1-mediated process that decreases ITPR3 expression in the cholangiocytes, which impairs secretion. This previously unrecognized pathway suggests new treatment targets.

AS081

Fecal microbial transplant reduces short-term cravings, improves quality of life and microbial diversity in cirrhosis and alcohol use disorder: a randomized, placebo-controlled, clinical trial

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Background and aims: An altered gut-liver-brain axis underlies alcohol use disorder (AUD). AUD can result in cirrhosis and often patients continue to drink despite cirrhosis development. Fecal microbiota transplant (FMT) can change gut microbiota & brain function in cirrhosis, but its effect on AUD is unclear. Aim: Define safety and effect on alcohol craving in cirrhotic pts with AUD who continue to drink in a clinical trial.

Method: Cirrhotic pts with AUD (AUDIT-10 score>8) with several unsuccessful attempts at rehabilitation, MELD<17, without alcoholic hepatitis were randomized 1:1 into placebo or FMT in a blinded randomized trial. FMT material was derived from one donor containing high relative abundance of *Lachnospiraceae* and *Ruminococcaceae*. FMT/placebo were administered once via enema. Visits were carried out at days 1, 8, 15 & 30 post-intervention. Safety, adverse events(AE) were inquired at every visit. Alcohol craving questionnaire (ACQ: high = worse), Sickness impact profile (SIP) for quality of life (QOL; has total, physical & psychosocial score, high = worse) & stool for 16S microbial analysis were obtained at baseline & day 15.

Results: 20 cirrhotic men with ongoing AUD (65 ± 6.4 yrs, MELD 8.9 ± 2.7) & median (IQR) AUDIT of 16.0(12.0) were enrolled.

Baseline: No differences were seen, MELD 9.5 vs 9.3, $p = 0.35$, age 67.1 ± 5.2 vs 62.9 ± 7.1, $p = 0.15$, AUDIT score, 15.5 ± 7.7 vs 16.7 ± 7.9, $p = 0.74$, SIP ($p > 0.05$ all) & ACQ,2.7 (1.8–4.7) vs 3.1(2.4–4.5), $p = 0.53$.

Course: 2 placebo-assigned pts needed urgent attention within 30 days (1 hyponatremia & 1 atrial fibrillation); none in the FMT group. One pt each from placebo & FMT dropped out before day 30. The FMT pt restarted problem drinking. No AEs or changes in safety labs were seen.

Craving/QOL: A significant reduction in alcohol craving & improvement in total & psychosocial SIP was seen only in the FMT group at day15 (Figure). No change in placebo group or in physical SIP was seen.

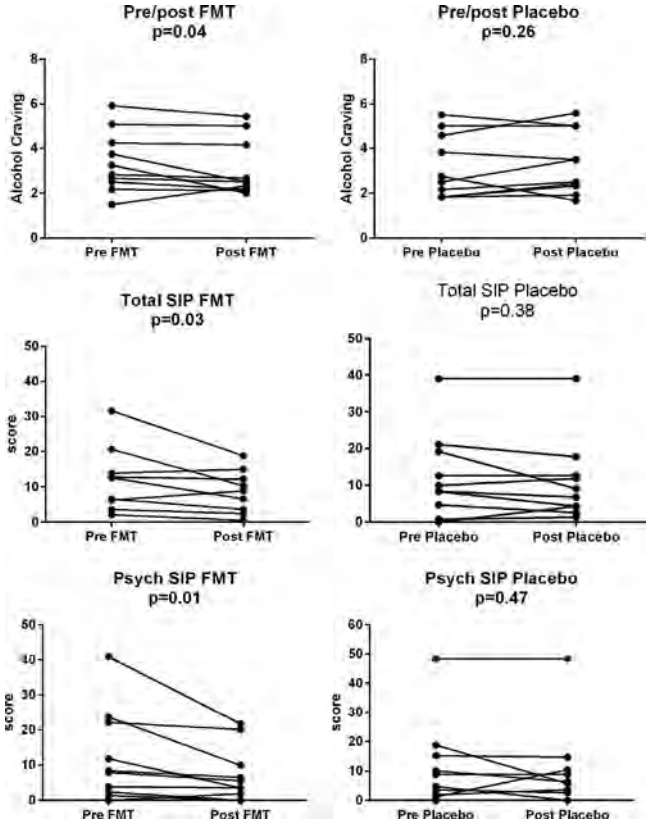

Figure: Changes in Alcohol Craving (high = worse) and Sickness Impact Profile (SIP) (high = worse) in baseline vs day 15 in placebo and FMT groups.

Microbiota: A significant increase in diversity was seen post-FMT vs baseline (1.67 ± 0.21 vs 1.83 ± 0.26, p = 0.29) but not in placebo (1.73 ± 0.30 vs 1.79 ± 0.19, p = 0.56). Unlike the others, diversity reduced vs baseline in the FMT pt who restarted problem drinking before day 30. At day 15, FMT pts had higher relative abundance of *Odoribacter* compared to baseline. At day 15, *Alistipes* and *Roseburia* were higher in FMT vs placebo.
Conclusion: Alcohol craving was significantly reduced accompanied by improvement in QOL after FMT in cirrhotic patients with AUD. These were associated with higher diversity & relative abundance of fatty acid producing taxa (*Roseburia, Alistipes & Odoribacter*) in FMT compared to placebo and baseline. Altering the gut-brain axis beneficially with FMT could be a potential avenue to alleviate AUD in cirrhosis.

AS082

Definition and prognostic relevance of the salve grading and staging system for alcohol-related liver disease

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Background and Aims: Alcohol misuse is among the most frequent causes of cirrhosis and liver transplantation. However, while elementary histologic features are well recognized a histologic grading and staging system specific for alcohol-related liver disease (ALD) is lacking. The Histopathology Group of the Consortium for the Study of Alcohol-related LiVer disease in Europe (SALVE) aimed to define a scoring system for the semiquantitative evaluation of grade (SALVE activity score, SAS) and fibrosis (SALVE fibrosis stage, SFS) intended for routine application and clinical studies.
Method: Interobserver variation and prognostic utility (endpoint: liver-related death) of the SAS and SFS system was assessed in a cohort of 172 biopsied patients comprising the whole clinical spectrum of ALD and long-term (5-year) follow-up.
Results: SAS is a combined score of macro vesicular steatosis (scores 0–2), hepatocellular ballooning (scores 0–2) OR Mallory-Denk bodies (scores 0–2), lobular neutrophils (scores 0–2), and cholestasis, the sum of canalicular and ductular cholestasis (CC and DC, respectively; both scored 0–1). Interobserver kappa of each grade feature was >0.6. Patients with alcoholic steatohepatitis (ASH) based on ballooning and neutrophil scores ≥ 1 and ASH with DC score 1 had a significantly worse 5-year survival compared to patients without ASH (p = 0.003, log-rank test). The SFS staging system is defined on a 4-step scale with respect to the type (dense portal-based and/or central-based pericellular fibrosis (PCF)) and extent of fibrosis allowing the subclassification of precirrhotic and cirrhotic SFS in several degrees of severity. Interobserver kappa for SFS was 0.86. Patients with SFS 3 and 4 showed significantly worse survival than patients with SFS 0–2 (p = 0.001, log-rank test). On multivariable Cox regression adjusted for bilirubin, INR, albumin, platelets, leukocytes, sodium, sex and abstinence, independent histological predictors of short-term (90 days) and long-term outcome were SFS (p = 0.01 and 0.004, respectively), CC (p = 0.028 and 0.034, respectively), and DC (p = 0.040 and 0.021, respectively).
Conclusion: The SALVE grading and staging system is a reproducible and prognostically relevant method for semiquantitative assessment of disease activity and fibrosis in ALD. Following validation, it may prove useful to stratify patients and evaluate therapeutic interventions.

AS083

The selective PPAR-delta agonist seladelpar reduces ethanol-induced liver disease by restoring gut barrier function and bile acid homeostasis in mice

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Background and Aims: Chronic alcohol-related liver disease is associated with dysregulation of bile acid metabolism and gut barrier dysfunction. PPAR-delta agonists are key metabolic regulators and anti-inflammatory agents. Here, we evaluated the effect of the selective PPAR-delta agonist seladelpar (MBX-8025) in a mouse model of ethanol-induced liver disease.
Method: Wild type C57BL/6 mice were fed a Lieber DeCarli diet containing 0% to 36% ethanol (caloric) for 8 weeks followed by one binge of ethanol (5 g/kg). Pair fed mice received an isocaloric liquid diet as control. Seladelpar (10 mg/kg/d) or vehicle was added to the liquid diet during the entire feeding period (prevention trial), or during the last four weeks of ethanol feeding (intervention trial).
Results: In both prevention and intervention trials, seladelpar protected mice from ethanol-induced liver disease, characterized by lower serum alanine aminotransferase levels and hepatic triglycerides. Chronic ethanol intake disrupted bile acid metabolism by increasing the total bile acid pool and secondary bile acids. Seladelpar reduced total serum bile acids, secondary serum bile acids and the total bile acid pool as compared with vehicle treatment in the prevention and intervention trials. Ethanol feeding is also associated with gut barrier dysfunction. Seladelpar stabilized the gut barrier function, characterized by lower fecal albumin in the prevention trial and lower serum lipopolysaccharides in the intervention trial. We confirmed that systemic blood ethanol levels were similar in all conditions, indicating that intestinal absorption and hepatic metabolism of ethanol are not affected by seladelpar. Furthermore, we confirmed that serum levels of seladelpar were similar in the ethanol treated mice, compared with the levels of seladelpar in the isocaloric control diet mice, indicating that ethanol did not affect exposure to seladelpar.
Conclusion: The selective PPAR-delta agonist seladelpar restored ethanol-induced gut barrier function, reversed dysregulation of bile acid metabolism and protected mice from ethanol-induced liver disease. The data from this study demonstrate that seladelpar prevents or treats ethanol-induced damage in mice by direct PPAR-delta agonism in both the liver and the intestine.

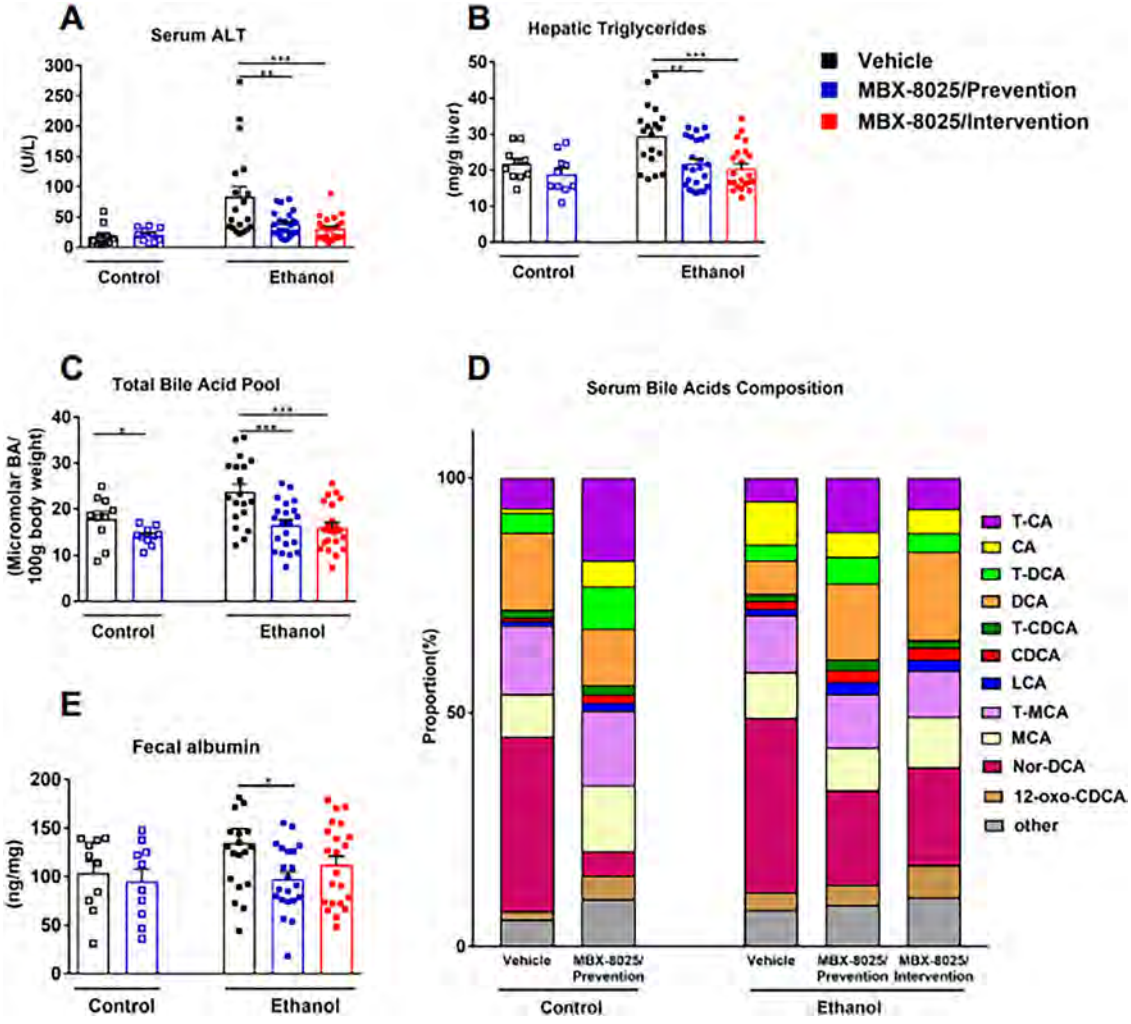

Figure: (abstract: AS083)

AS084

Genetic variation in HSD17B3 reduces the risk for developing severe alcoholic hepatitis

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Background and Aims: Carriage of *PNPLA3*:rs738409:G increases the risk for developing severe alcoholic hepatitis. Carriage of *HSD17B13*:rs72613567:TA decreases the risk for developing alcohol-related cirrhosis and HCC and attenuates the risk associated with *PNPLA3*:rs738409:G. The aims of this study were to: (i) determine the effect of rs72613567 on the risk for developing severe alcoholic hepatitis and the risk relationship between rs72613567A and rs738409; and (ii) examine for associations between these gene variants, disease severity, and markers of epithelial cell death.

Method: Genotyping for rs738409 and rs72613567 was undertaken in 3511 subjects including: 898 participants in the STOPAH trial; 327 with alcohol-related cirrhosis; 1911 alcohol misusers with no liver injury; and, 1095 healthy controls. Genetic associations with the risk for developing severe alcoholic hepatitis were determined; the relationships between genotype, disease severity and serum markers of epithelial cell death (CK18M30 and CK18M65) were explored; population attributable fractions (%PAF) were calculated for both variants.

Results: Carriage of rs738409:G was associated with an increased risk for developing severe alcoholic hepatitis (OR: 1.85 [95% CI: 1.58–2.16], $p = 8.4^{e-15}$), while carriage of rs72613567:TA was associated with a decreased risk (OR: 0.85 [95% CI: 0.74–0.98]; p = 0.029). The % PAFs associated with carriage of rs738409:G and rs72613567:TA were 25.5% [17.2 to 34] and −6.3% [−15.8 to 3.5] with a combined %PAF of 20.8% [4.1 to 36.3] indicating attenuation of the effect of rs738409:G by rs72613567:TA. Carriage of rs72613567:TA was associated with lower prothrombin times (β −0.9445, SE: 0.3132, p = 0.0026), lower Maddrey DF (β: −4.369, SE: 1.49, p = 0.0035) and GAH scores (OR: 0.80 [95% CI: 0.64–0.99], p = 0.039) and lower serum concentrations of CK18M30 (β: −801, SE: 264.6, p = 0.003) and CK18M65 (β: −1092, SE: 328.9, p = 0.0009) (Figure). Survival at 28 days and 90 days was not influenced by either variant.

Conclusion: Carriage of *PNPLA3*:rs738409:G and *HSD17B13:* rs72613567:TA differentially affect the risk for developing severe alcoholic hepatitis. Carriage of rs72613567:TA is associated with less severe liver dysfunction, lower disease severity scores and a reduction in serum CK18 fragments suggesting that its protective effect is ultimately mediated *via* a reduction in hepatocyte death.

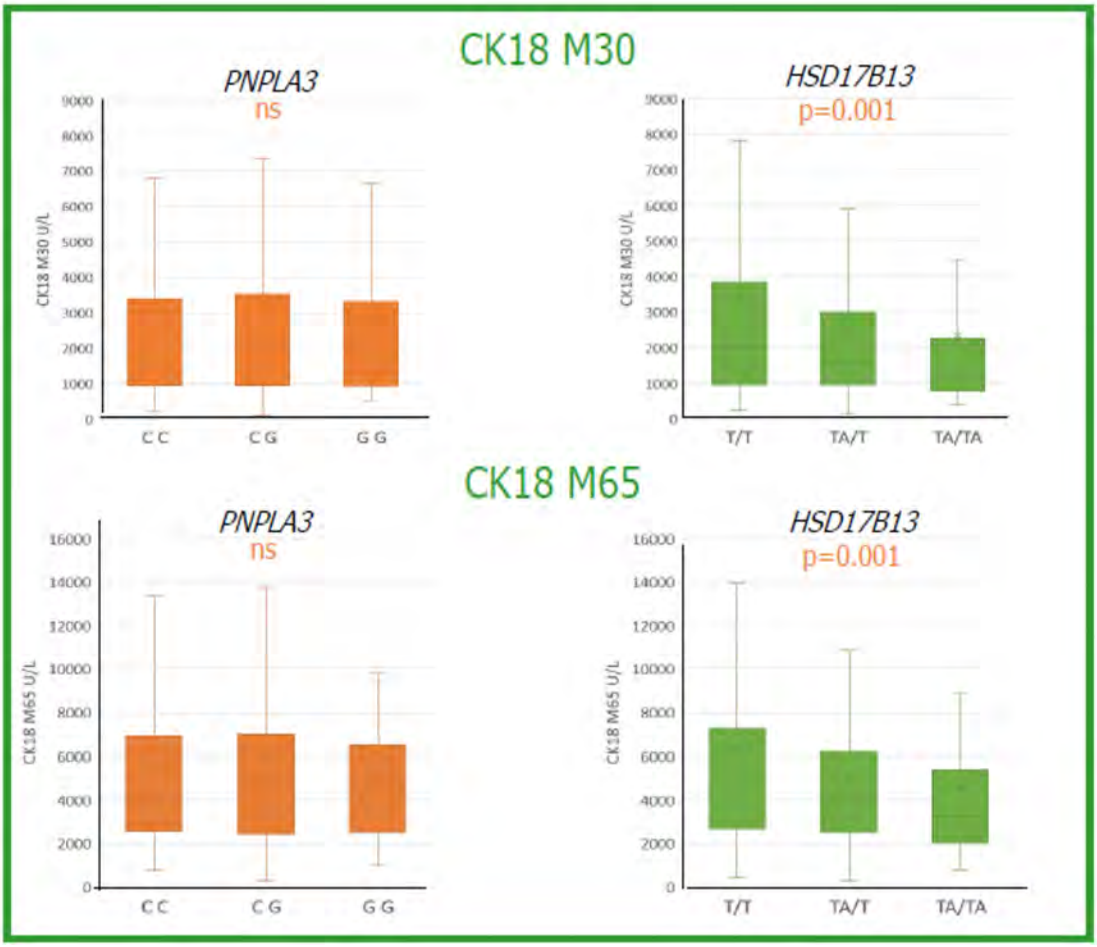

Figure: (abstract: AS084): Serum CK18M30 and M65 in alcoholic hepatitis, by genotype.

Rare liver disease

AS085

Twelve-month interim analysis of efficacy and safety of givosiran, an investigational RNAi therapeutic for acute hepatic porphyria, in the envision open label extension

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Background and Aims: Acute hepatic porphyria (AHP) is a family of rare genetic diseases due to enzyme defects in hepatic heme biosynthesis. Induction of 5-aminolevulinic acid synthase 1 (ALAS1), the rate-limiting step in heme biosynthesis, can lead to accumulation of toxic heme intermediates 5-aminolevulinic acid (ALA) and porphobilinogen (PBG), causing neurovisceral attacks and chronic manifestations. Givosiran, an investigational RNAi therapeutic, targets liver ALAS1 to reduce ALA/PBG and ameliorate attacks and clinical manifestations.
Method: ENVISION (NCT03338816) is an ongoing Phase 3 global, multicenter, randomized, placebo-controlled trial, evaluating the efficacy and safety of subcutaneous monthly doses of 2.5 mg/kg givosiran in AHP patients in a 6-month double-blind (DB) period and an open label extension (OLE) period (up to 30 months). During the OLE, patients received either 2.5 mg/kg or 1.25 mg/kg monthly givosiran. Outcome measures included composite annualized attack rate (AAR) requiring hospitalization, urgent care, or IV-hemin at home, ALA/PBG levels, hemin use, daily worst symptoms, and quality of life (QoL). Analyses were descriptive.
Results: As of July 23, 2019, 93 patients entered the OLE: 56 (placebo/givosiran = 29; givosiran/givosiran = 27) received 2.5 mg/kg monthly givosiran, and 37 (placebo/givosiran = 17; givosiran/givosiran = 20) received 1.25 mg/kg. In givosiran patients (both doses), median AAR was 1.1 (range: 0–20.5) through Month 12. In placebo patients who crossed over to givosiran in the OLE, median AAR (DB = 10.65; OLE = 1.81) and proportion of attack-free patients (DB = 17.4%; OLE = 42.2%) were similar to the givosiran group in the DB period (median AAR = 1.04; attack free patients = 48.9%). In addition, sustained lowering of ALA/PBG in the OLE was accompanied by reductions in hemin use, daily worst pain and analgesic use, and improvements in QoL. Among patients on givosiran through Month 12, 62% had ≥ 1 drug-related adverse event (AE) and 3% had ≥ 1 drug-related serious AE. There were no new AEs leading to discontinuation and no deaths. No new safety concerns occurred in the OLE. There was a trend toward increased efficacy with the 2.5 mg/kg dose compared to 1.25 mg/kg dose, and safety was acceptable at both doses.
Conclusion: In an ongoing Phase 3 study, givosiran 2.5 mg/kg monthly demonstrated maintenance or enhancement of clinical efficacy and an acceptable safety profile consistent with that observed in the 6-month DB period.

AS086
Primary liver cancer in acute hepatic porphyria: a national cohort study

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Background and Aims: The porphyrias are a group of diseases caused by defects in the different enzymes of the heme synthesis pathway. In acute intermittent Porphyria (AIP), Variegate Porphyria (VP) and Hereditary Coproporhyria (HCP), commonly grouped as acute hepatic porphyrias (AHP), increased levels of 5-aminolevulinic acid (ALA) and porphobilinogen (PBG) are associated with the typical acute neurovisceral attacks. Previous studies show that AHP-patients carry an increased risk of primary liver cancer (PLC). However, risk estimates are uncertain, and little is known about how AHP subtype, AIP mutation, biochemical activity or disease severity affect the risk. Our aim was to assess the risk of PLC in correlation to these variables in a large population-based cohort.
Method: All patients in the Swedish porphyria registry with verified AIP, VP and HCP were included and matched to reference individuals from the general population 1:10 by age, sex and municipality. Data on incident PLC were collected from national health registries and validated by a set of criteria to minimize risk of misclassification. PLC incidence were compared by incidence rate ratio. For the AIP-subgroup, data were collected on type of HMBS-mutation, maximal U-PBG and number of hospitalizations for porphyria.
Results: We identified 1244 patients with AHP between 1987 and 2015, of which 1063 (85%) had AIP. Health registries identified 108 subjects with a verified PLC diagnosis, 83 among AHP patients (6.7%) and 25 among reference individuals (0.2%), corresponding to an incidence risk ratio of 34.2 (95% confidence interval:21.9–53.5). For the AIP subgroup, elevated U-PBG levels and hospitalizations for porphyria, but not mutation, were associated with an increased PLC risk. AIP patients >50 years of age with a previously recorded elevated U-PBG (n = 158) had an annual PLC-incidence rate of 1.8%. There was only one case of PLC in the VP (n = 125) and one case in the HCP (n = 56) group, indicating a low risk for incident PLC compared to AIP.
Conclusion: Patients with AIP have a markedly increased risk of PLC compared to a matched reference group. The increased risk is associated with biochemical and clinical activity but not with mutation.

AS087
Variants in PCSK7, PNPLA3 and TM6SF2 are risk factors for the development of cirrhosis in people with hereditary haemochromatosis

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	Nr	Primary liver cancers found	Rate ratio (95% CI)	Incidence rate (per 1000/ year)
Controls	12333	25	NA	0.11
AHP-cases	1244	83	34.2 (21.9-53.5)	3.85
- AIP	1063	81	38.2 (24.4-59.8)	4.30
- VP	125	1	5.1 (0.7–37.5)	0.57
- HCP	56	1	6.1 (1.3–68.1)	1.04

Figure: (abstract: AS086)

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Background and Aims: Cirrhosis develops in <10% of individuals with hereditary haemochromatosis homozygous for the C282Y variant in the *homeostatic iron regulator* (*HFE*) gene. Carriage of *PCSK7*:rs236918:C is known to be associated with an increased risk for developing cirrhosis in this population. This study aimed to determine if carriage of variants associated with the risk for developing alcohol- and NAFLD-related cirrhosis, *viz PNPLA3*: rs738409, *TM6SF2*:rs58542926, *MBOAT7*:rs641738, and *HSD17B13*: rs72613567, also modulate the risk for developing cirrhosis in C282Y homozygotes.

Methods: Variants in *PCSK7, PNPLA3, TM6SF2, MBOAT7, and HSD17B13* were genotyped in 1337 C282Y homozygotes, from six European countries, of whom 181 (13.5%) had established cirrhosis. Genotypic and allelic associations with the risks for developing cirrhosis were assessed using logistic regression analysis, adjusting for age and sex. Fixed-effect meta-analyses of the adjusted summary data for each country were performed. Post-hoc testing was undertaken in 137 (75.7%) cases and 284 (24.6%) controls with available liver histology. Population-attributable fractions (%PAFs) were calculated for any significantly associated alleles.

Results: Significant associations were observed between *PCSK7:* rs236918 (OR = 1.44 [95% CI 1.01–2.05]; p = 0.042; I^2 = 0%); *PNPLA3:* rs738409 (OR = 1.60 [95% CI 1.22–2.09]; p = 5.9×10^{-4}; I^2 = 65.9%) and *TM6SF2:*rs58542926 (OR = 1.80 [95% CI 1.20–2.70]; p = 4.8×10^{-3}; I^2 = 0%) and the risk for developing cirrhosis in C282Y homozygotes. These findings remained significant in the subpopulations with available liver histology. The PAFs were 4.9% for *PCSK7*:rs236918:C; 13.8% for *PNPLA3*:rs738409:G, 5.7% for *TM6SF2*:rs58542926:T, and 22.7% for carriage of all three variants combined. The associations with *MBOAT7*:rs641738, and *HSD17B13*:rs72613567 were not significant (Figure).

Conclusion: The risk for developing cirrhosis associated with carriage of *PCSK7*:rs236918 was confirmed in this large, well-characterized population of C282Y homozygotes. In addition, *PNPLA3*:rs738409 and *TM6SF2*:rs58542926 were established as significant additional risk modulators. More detailed genetic testing and use of genotypic-phenotypic risk scores could identify C282Y homozygotes at particular risk for developing cirrhosis and facilitate their management.

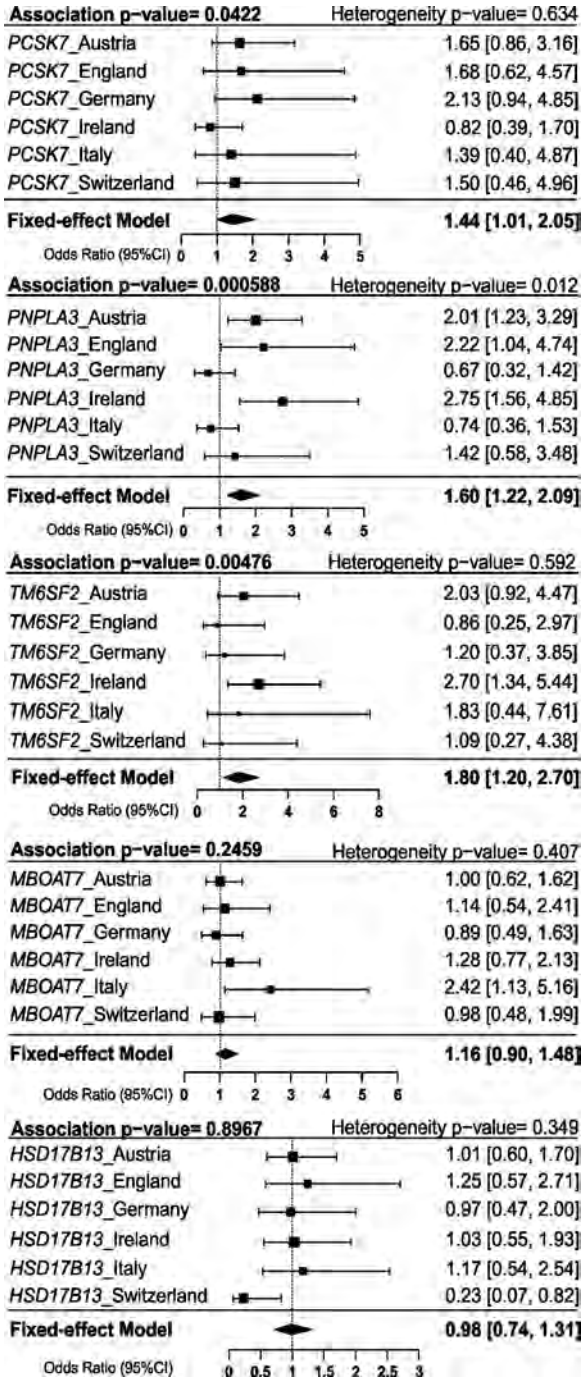

Figure: (abstract: AS087): Genotypic associations with the risk for developing cirrhosis in C282Y homozygotes, adjusted for age, sex, by country.

AS088

Natural history of polycytemia vera and essential thrombocythemia presenting with splanchnic vein thrombosis

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Background and Aims: Polycythemia vera (PV) and essential thrombocythemia (ET) are myeloproliferative neoplasms (MPN) characterized by an increased risk of thrombosis. In a minority of these patients, splanchnic venous thrombosis (SVT) is the first manifestation of the disease. These patients appear to have different biological/phenotypic characteristics from the remaining patients with PV/ET (they are younger, predominantly female and with lower JAK2V617F mutational load). However, their natural history has not been well described.
The objective of this study was to characterize the natural history of patients with PV/ET in whom SVT is the first clinical manifestation in comparison to patients with the same age/sex without this complication at diagnosis.
Method: Patients with PV and ET with SVT as first manifestation were identified from three prospective multicenter national registries (PV Registry, ET Registry and Spanish registry of hepatic vascular diseases (REHEVASC). Of a total of 3705 patients with PV/ET, 118 (3.2%) presented SVT as the first manifestation. Survival was the main objective of the study and risk of retrombosis, bleeding, disease progression or the appearance of second malignancies were secondary objectives. COX regression analysis adjusted for age, sex and presence of SVT as first manifestation was used.. Competing risk analysis was used for analyzing secondary objectives.
Results: Patients with PV/ET with SVT as first manifestation (25 Budd-Chiari Syndrome (BCS), 74 splenoportal thrombosis (PVT), 3 mixed cases (SBC + PVT) and 16 unspecified) were significantly younger, with a PV predominance and with a lower prevalence of cardiovascular risk factors. These patients had an increased risk, adjusted for age and sex, of death (HR: 2.47, 95% CI: 1.5–4.01, $p < 0.001$), venous thrombosis (IRR: 3.4, 95% CI: 2.1–5.5, $p < 0.001$), of a second malignancy (IRR: 2.4, 95% CI: 1.4–4.2, $p = 0.002$) and major bleeding (symptomatic bleeding in a critical or asymptomatic organ associated with need for transfusion or a hemoglobin drop of >20 g/L: IRR: 7.2, 95% CI: 4.3–12.1, $p < 0.001$). No cases of leukemic transformation were documented among these patients and 7 (6%) progressed to myelofibrosis after a mean follow-up of 6 years.
Conclusion: Patients with PV and ET who had SVT as a first manifestation have a reduced survival compared to those patients with PV/TE without SVT of their same age and sex. The excess mortality seems to be more related to the liver disease itself, the higher incidence of bleeding and the appearance of second malignancies than with the evolution of the base PV/ET.

AS089

Remarkable long-term outcome of step-wise management strategy for Budd-Chiari syndrome in China: a nationwide 20-year retrospective study of 1366 patients

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Background and Aims: There lacks comprehensive data of step-wise strategy for Budd-Chiari syndrome (BCS) in typical Asian countries, despite a higher prevalence and greater demand for in-depth studies in this region. We conducted this nationwide study to investigate the possibly different roles of angioplasty and transjugular intrahepatic portosystemic shunt (TIPS) in the whole picture of step-wise strategy as well as their efficacy and safety profiles.
Method: A total of 1366 consecutive BCS patients admitted to six Chinese tertiary hospitals and received management conforming to step-wise principle from July 1998 to May 2019 were included. The last follow-up ended on July 15th, 2019.
Results: Median follow-up was 64 (36–100) months. The 10-year OLT-free survival was 79.1% (76.2–82.0%); TIPS-OLT-free survival 72.1% (69.2–75.2%); stenting-TIPS-OLT free survival 45.8% (42.6–49.2%); and the intervention-free survival 6.0% (4.5–7.9%, Fig. A). All patients received medical treatment and 169 (12.4%) had no further procedures. A total of 1137 (83.2%) patients received angioplasty (435 [38.3%] with initial stenting and 702 [61.7%] without). Although 10-year survival did not differ (80.0% [75.5–84.7%] vs. 83.3 [79.3–87.5%], log-rank $p = 0.653$), initial stenting reduced 10-year restenosis (23.1% [17.8–28.1%] vs. 34.4% [28.8–39.5%], log-rank $p < 0.001$, Fig. B) and symptom recurrence rate (21.7% [16.6–26.5%] vs. 30.0% [24.2–35.4%], log-rank $p = 0.015$, Fig. C). Stent-related complications occurred in 11 (2.5%), with an event-free survival in all but one patient who died of intracranial bleeding. TIPS was performed in 126 (9.2%) patients (57 initial TIPS, and 69 converted TIPS), with 22 (17.5%) bare TIPS and 104 (82.5%) covered TIPS. Covered TIPS significantly lowered shunt dysfunction rate (51.1% [37.3–61.8%] vs. 70.4% [40.4–85.3%] at 5 years, log-rank $p = 0.038$, Fig. D), but did not improve recurrence rate (76.8% [62.7–85.5%] vs. 79.4% [46.4–92.1%] at 5 years, log-rank $p = 0.647$, Fig. E) or survival (64.8% [51.2–81.9%] vs. 57.7% [39.9–83.3%] at 10 years, log-rank $p = 0.621$). Only 1 (0.1%) patient with progressive liver failure received transplantation and died 27 days later due to multiple organ failure.
Conclusion: The current study corroborated that step-wise strategy can achieve remarkable long-term outcome in typical Chinese BCS patients, yet the predominant application of angioplasty with or without stenting contributed over 80% survival benefits while TIPS contributed 10%, constituting an inverted proportion of European reports. Moreover, the patency and efficacy of angioplasty could be boosted with initial stenting with adequate safety, whereas TIPS is less liberally used and can be eventful with high dysfunction and symptom recurrence rates even with covered stents, thus the optimal indication and candidates of early-TIPS still require cautious investigation.

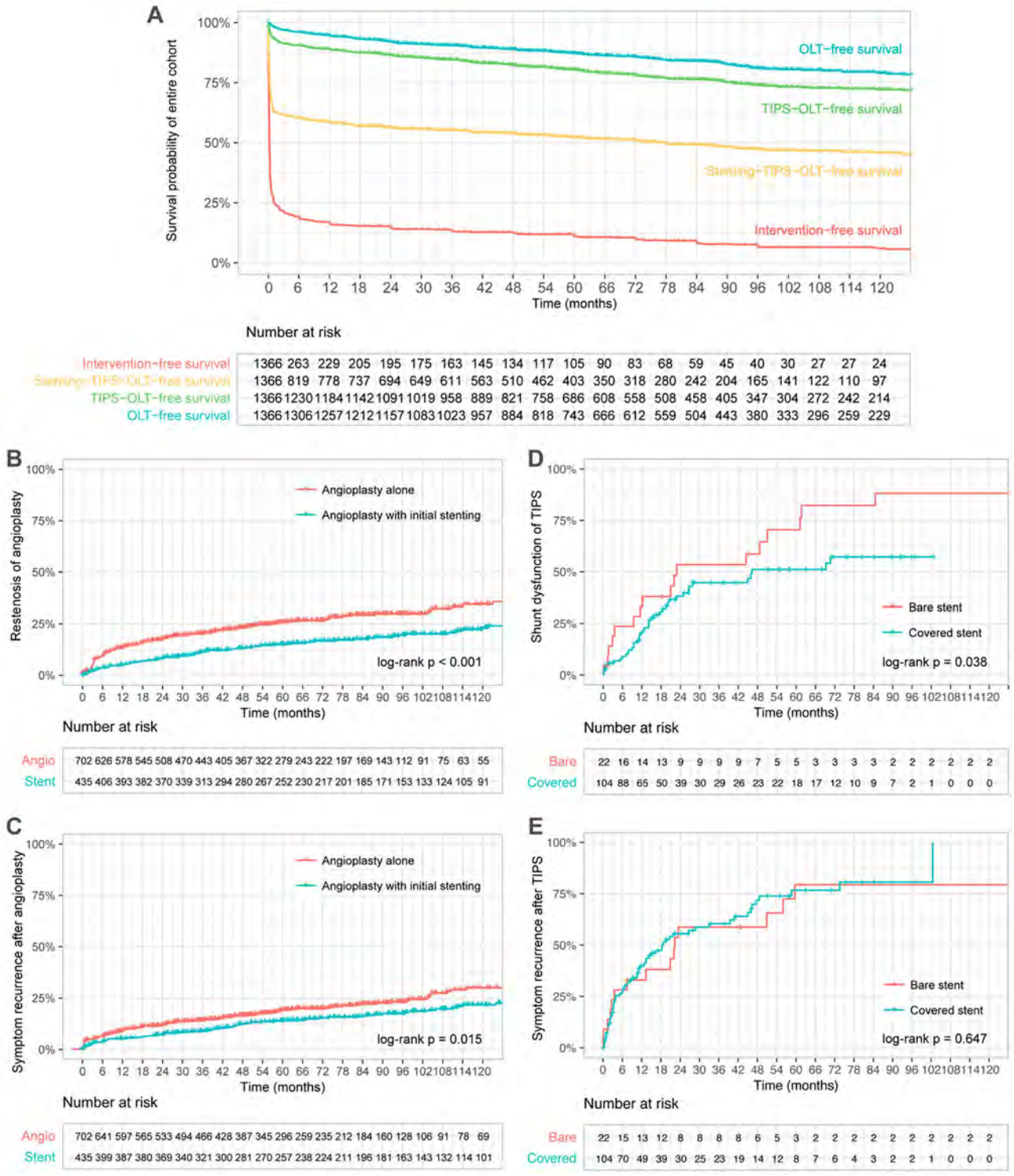

Figure: (abstract: AS089)

AS090

Liver disease in common variable immunodeficiency (CVID) is characterised by a high frequency of portal hypertension and significant burden of inflammatory liver pathology

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Background and Aims: CVID is characterised by impaired B-cell function and hypogammaglobinaemia. There is heterogeneity in organ involvement which may manifest as granulomatous, infective,

autoimmune or malignant processes. Here we describe the frequency, severity and natural history of liver disease, which are relatively unexplored, in the largest cohort of patients with CVID reported to date.

Method: Patients with CVID were identified from the Royal Free Hospital Immunology database. Liver involvement was defined as: i) persistently elevated liver enzymes ii) imaging features of chronic liver disease, or iii) splenomegaly or thrombocytopaenia with features of portal hypertension (PHTN).

Results: 220 patients with CVID were identified, of which 76 (34.5%) had liver involvement. The median age of patients with liver involvement was 53.5 (IQR 43.5–64) and 59% were female, compared to 53 (IQR 40.8–67) years and 53% female for those without. Elevated liver enzymes, either progressively worsening or intermittently elevated, were observed in 72/76 (95%) patients.

10 (13%) patients with liver disease had radiological features of PHTN and 12 /20 (60%) patients who underwent OGD had varices. Hepatic venous pressure gradients (HVPG) were measured in 20 patients, 14 (70%) had portal hypertension (≥ 5 mmHg) and 5 (25%) had significant portal hypertension (≥ 10 mmHg). 35 patients underwent liver biopsy; 12 (35%) had features of nodular regenerative hyperplasia (NRH), 7 (20%) had granulomata and 8 (23%) had moderate to severe inflammatory activity.

9 (12%) patients with liver disease had histologically proven cirrhosis, of which 6 had end-stage liver disease (ascites or variceal bleeding). The median age of those with cirrhosis was 50 and the number of years between diagnoses of CVID and cirrhosis was 11 (IQR 8–12).

Crude mortality rates were higher amongst CVID patients with liver involvement than those without (19.1% vs 13.1%). 2 deaths occurred due to decompensated liver disease and one patient underwent liver transplantation.

Conclusion: In this study of the largest CVID cohort to date, we have demonstrated that liver involvement is a frequent occurrence and is associated with a high frequency of PHTN. Histologically, NRH and granulomatous disease are common and, notably, moderate-severe inflammatory infiltrates are common, hence evaluation of any role for immunosuppression in CVID-related liver disease is needed. Patients with CVID and liver involvement have a poor prognosis and liver disease should be actively sought out and patients offered comprehensive assessment and dedicated follow up.

HBV – Clinical

AS091

A phase 3 study comparing switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) with continued TDF treatment in virologically-suppressed patients with chronic hepatitis B (CHB): final week 96 efficacy and safety results

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Background and Aims: We have previously demonstrated at Week 48 that switching to TAF vs continued TDF treatment in CHB patients who were virally suppressed on long-term TDF has shown noninferior efficacy of TAF to TDF with superior bone and renal safety. Here we report the final, efficacy and safety results from this study at Week 96.

Method: In this Phase 3 study (NCT02979613), CHB patients taking TDF for ≥48 weeks with HBV DNA <LLOQ (local lab) for ≥12 weeks and <20 IU/mL at screening were randomized (1:1) to TAF 25 mg QD or TDF 300 mg QD, each with matching placebo, and treated for 48 weeks in a double-blind (DB) fashion. At Week 48, all patients received open-label (OL) TAF 25 mg once daily for an additional 48 weeks. Safety assessments including changes in bone (hip and spine BMD) and renal (CrCl by Cockcroft-Gault [$eGFR_{CG}$], serum creatinine) parameters; viral suppression, and serological and biochemical responses were also assessed in all patients.

Table. Efficacy and Safety at Week 96 in CHB Patients Treated with TAF for 2 Years vs TDF Treatment for 1 Year Followed by 1 Year of TAF

N (%) or n/N (%)	TAF-TAF (N=243)	TDF-TAF (N=245)	P value
Efficacy parameters[a]			
HBV DNA <20 IU/mL	230 (95)	230 (94)	
Difference in proportions (95% CI)	0.9% (-3.5% to 5.2%)		0.686
ALT normalization[b]	29/52 (56)	39/53 (74)	0.051
HBeAg loss / seroconversion[c]	14/78 (18) / 4/78 (5)	7/78 (9) / 2/78 (3)	0.101 / 0.415
HBsAg loss / seroconversion	4 (2) / 2 (1)	6 (2) / 1 (0.4)	0.537 / 0.585
Safety parameters			
Hip BMD, mean (SD) % change (g/cm²)	1.16 (2.85)	0.18 (2.68)	<0.001
Spine BMD, mean (SD) % change (g/cm²)	2.33 (3.93)	1.73 (3.82)	0.097
CTX, median (Q1, Q3) % change (ng/mL)[d]	-25 (-38.2, -5.1)	-24.1 (-42.2, -6.9)	0.635
P1NP, median (Q1, Q3) % change (ng/mL)[e]	-17.9 (-30.7, -3.2)	-21.4 (-37.7, -6.8)	0.017
$eGFR_{CG}$, median (Q1, Q3) change (mL/min)	+0.51 (-5.98, 5.32)	-0.39 (-6.76, 6.28)	0.871
RBP/Cr, median (Q1, Q3) % change[f]	-19.7 (-41.7, 23.2)	-13.4 (-41.5, 29.4)	0.304
β2MG/Cr, median (Q1, Q3) % change[g]	-32.6 (-67.1, -7.2)	-37.5 (-68.4, 4.3)	0.935

[a]All efficacy results are missing=failure. TAF-TAF and TDF-TAF are DB TAF to OL TAF and DB TDF to OL TAF, respectively. [b]AASLD ULN 33 U/L males, 25 U/L females; [c]Patients who were HBeAg-positive at baseline; [d]C-type collagen sequence (bone resorption marker); [e]Procollagen type 1 N-terminal propeptide (bone formation marker); [f]Retinol binding protein/creatinine (tubular marker); [g]Beta-2 microglobulin/creatinine (tubular marker)

Results: Of 488 (TAF 243, TDF 245) patients randomized and treated, 472 (97%; TAF 235, TDF 237) completed 48 weeks of DB treatment, and 465 (95%; TAF 233, TDF 232) completed study treatment through Week 96. At baseline, patient characteristics were similar between groups and have been previously reported. Key efficacy/safety results are summarized in the Table. Virologic suppression (HBV DNA <20 IU/mL) was similarly maintained at Wk96 in patients switched to TAF treatment at BL vs those switched to TAF after 48 weeks of DB TDF treatment; rates of ALT normalization were increased in both groups at Wk 96. In patients switched to TAF at BL vs those switched at Wk48, similar increases in spine BMD were seen while increases in hip BMD were smaller. In the TDF group, $eGFR_{CG}$ decreased at Wk48 (−2.7 mL/

min); an improvement was seen after switching to TAF at Wk96 (–0.39 mL/min).
Conclusion: In CHB patients on long-term TDF treatment, viral suppression was maintained, ALT normalization increased, and bone and renal safety parameters were improved at Wk 96.

AS092
Immune checkpoint inhibitors and hepatitis B viral kinetics – a territory-wide cohort study

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Background and Aims: Immunotherapy using immune checkpoint inhibitors (ICI) have dramatically improved the survival of patients with advanced or metastatic malignancies. Recent studies suggest that the new programmed death receptor 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors have potential in the treatment of patients with chronic HBV infection. We evaluated the kinetics of hepatitis B virus (HBV) in patients with chronic hepatitis B or past HBV infection.
Method: This was a territory-wide retrospective observational cohort study in Hong Kong. We identified patients through the Clinical Data Analysis and Reporting System (CDARS) based on the drug record of immune checkpoint inhibitors from 1 January 2014 to 31 October 2018. Patients who were hepatitis B surface antigen (HBsAg)-positive or HBsAg-negative but antibody to hepatitis B core antigen (anti-HBc) positive were included.

No. of subjects	HBsAg positive N = 237	HBsAg negative, anti-HBc positive N = 158
Male gender (n, %)	200 (84.4)	110 (69.6)
Age (years)	57.9 ± 12.1	62.9 ± 11.5
Platelet (x10^9/L)	218.1 ± 120.5	231.4 ± 153.4
International normalized ratio	1.1 ± 0.1	1.1 ± 0.2
Missing (%)	6.8	6.3
Albumin (g/l)	36.4 ± 6.9	36.6 ± 7.1
Total bilirubin (μmol/l)	30.7 ± 70.3	12.8 ± 37.1
Alanine aminotransferase (ULN)	0.8 (0.5-1.6)	0.6 (0.4-0.9)
Alkaline phosphatase (ULN)	1.0 (0.7-2.1)	0.8 (0.6-1.1)
Aspartate aminotransferase (ULN)	1.2 (0.8-3.2)	0.8 (0.5-1.0)
Missing (%)	16.1	35.4
Creatinine (umol/L)	80.5 ± 80.2	91.5 ± 67.5
Alpha-fetoprotein (μg/l)	70.5 (3.5-3506.6)	2.9 (2.0-4.9)
Missing (%)	15.2	63.3
Positive HBeAg (n, %)[D]	15 (11.9)	0 (0)
Missing (%)	46.8	95.6
HBV DNA (log_{10} IU/mL)	1.9 ± 1.9	0.06 ± 0.3
Missing (%)	38.8	43.7
Antiviral treatment (n, %)[#]		
Lamivudine	12 (5.1)	1 (0.6)
Adefovir Dipivoxil	4 (1.7)	0 (0)
Entecavir	210 (88.6)	43 (27.2)
Telbivudine	9 (3.8)	0 (0)
Tenofovir*	24 (10.1)	0 (0)
Any nucleos(t)ide analogues	230 (97.0)	44 (27.8)
(Pegylated)-interferon	1 (0.4)	1 (0.6)
HBV reactivation (n, %)		
ALT > 2xULN	44 (31.0)*	27 (22.3)**
ALT > 5xULN	18 (12.7)*	14 (11.6)**
HBV DNA > 2,000 IU/mL	2 (1.7)[&]	0 (0)[^]
HBV DNA increase > 1 log	6 (4.1)[&&]	0 (0)[^^]

Upper limit of normal (ULN) of ALT and AST was set at 40 IU/mL.
[D] Percentages were based on non-missing data.
[#] All comorbidities and concomitant medications were represented as binary parameters.
* Among 142 patients who had ALT < ULN at the start of immunotherapy.
** Among 121 patients who had ALT < ULN at the start of immunotherapy.
[&] Among 116 patients who had HBV DNA <2000 IU/mL at the start of immunotherapy.
[&&] Among 145 patients who had available HBV DNA at the start of immunotherapy.
[^] Among 89 patients who had HBV DNA <2000 IU/mL at the start of immunotherapy.
[^^] Among 89 patients who had available HBV DNA at the start of immunotherapy.
Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, and alpha-fetoprotein were expressed in median (interquartile range), whereas other continuous variables were expressed in mean ± standard deviation.

Figure: Hepatitis B reactivation after immunotherapy.

Results: 395 patients (237 HBsAg-positive and 158 HBsAg-negative/antiHBc-positive) were identified (male 84% and 70%; mean age 58 and 63 years; mean HBV DNA 1.9 and 0.06 log10 IU/mL respectively). 97% of HBsAg-positive and 28% HBsAg-negative/antiHBc-positive patients were put on oral antiviral treatment. Hepatitis flare (ALT >2× ULN) occurred in 31% of HBsAg-positive and 22% HBsAg-negative/antiHBc-positive patients; severe hepatitis flare (ALT >5× ULN) 13% and 12% respectively. HBV DNA increased to >2,000 IU/mL or >1 log10 IU/mL in 2 and 6 HBsAg-positive subjects respectively; whereas none of the HBsAg-negative/antiHBc-positive subjects had such HBV reactivation. No HBsAg-positive patients cleared HBsAg and no HBsAg-negative/antiHBc-positive patients had HBsAg seroreversion during follow-up period.
Conclusion: HBV reactivation is rare in patients received immunotherapy in patients with chronic hepatitis B or past HBV infection. None of our patients achieved HBsAg seroclearance after immunotherapy.

AS093
Characterization of serologic responses following ALT flares in >3000 CHB patients pooled from 5 clinical trials

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Background and Aims: ALT flares in patients treated for Chronic Hepatitis B (CHB) infection have been associated with improvements in viral parameters. The timing, frequency, severity and consequences of these elevations in ALT have not been completely characterized. Here, we pool data from 5 Phase 3 studies evaluating tenofovir-based regimens to determine the associations of ALT flares with different treatment outcomes.
Method: Clinical data from 5 studies (GS-US-174-102, GS-US-174-103, GS-US-174-0149, GS-US-320-0108, and GS-US-320-0110) were evaluated for the presence of ALT flares on treatment, defined as ALT >5× ULN and >2× Baseline (Low Flares) or ALT >10× ULN and >2× Baseline (High Flares). Endpoints of HBsAg loss, HBeAg loss, and HBsAg decline of >=1log_{10} were evaluated at 12, 24, or 48 weeks after the flare.
Results: The overall population was 3013 patients of whom 70% were Asian and 67% were male. Overall, 58% were HBeAg positive at baseline and 8%, 22%, 41%, and 27% had Genotype A, B, C, and D infection, respectively. Of these subjects, Low Flares were observed in 297 (9.9%) subjects with High Flares observed in 141 (4.7%) patients; the median week (Q1,Q3) to ALT flare was 8 (4, 59) for low flare and 14 (4,61) for high flare. In the overall population, HBeAg and HBsAg loss was observed in 634 and 93 subjects, respectively, during the treatment phase. The rates of serologic outcomes following these flares are shown in the table. Briefly, the presence of low and high flares were associated with increased rates of serologic outcomes that increased with longer duration follow-up. Rates of serologic outcomes were observed more often in patients having higher flares, though the higher flares identified overall fewer cases of patients achieving the clinical endpoints. Interestingly, the majority of patients with HBeAg loss and HBsAg loss did not have a measured ALT flare in the preceding 48 weeks of treatment.

Timepoint Post Flare	Outcome, n/N (%)	Low Flare	High Flare
Week 12	HBsAg loss	7/297 (2.4%)	4/141 (2.8%)
	HBsAg decline >=1 log_{10}	78/278 (28%)	52/131 (40%)
	HBeAg loss	25/206 (12%)	13/99 (13%)
Week 24	HBsAg loss	12/297 (4.0%)	6/141 (4.3%)
	HBsAg decline >=1 log_{10}	95/289 (33%)	59/135 (44%)
	HBeAg loss	38/206 (18%)	20/99 (20%)
Week 48	HBsAg loss	21/297 (7.1%)	13/141 (9.2%)
	HBsAg decline >=1 log_{10}	114/293 (39%)	65/137 (47%)
	HBeAg loss	63/206 (31%)	37/99 (37%)

Conclusion: Serologic outcomes of HBeAg loss and HBsAg decline and loss occurred following on-treatment ALT flares. These data demonstrate that the majority of patients achieved clinical endpoints 24 weeks after the ALT flare, though additional follow-up may identify more patients achieving these endpoints. These data inform current strategies for achieving important clinical outcomes for CHB patients, and suggest that some patients can achieve HBsAg/HBeAg loss without ALT flares.

AS094

Tenofovir vs entecavir on post-operative recurrence-free and overall survival of patients with hepatitis B virus-related hepatocellular carcinoma

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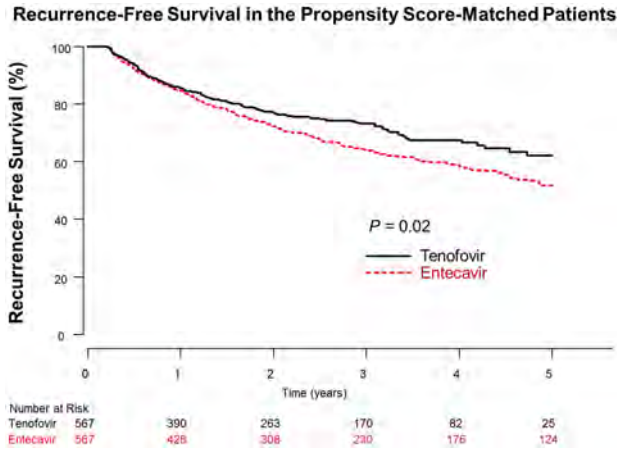
Background and Aims: Studies have suggested that tenofovir disoproxil fumarate (TDF) treatment was associated with a significantly lower risk of hepatocellular carcinoma (HCC) occurrence compared to entecavir therapy in chronic hepatitis B patients. We aimed to compare tenofovir and entecavir on the recurrence-free and overall survival of patients after curative hepatectomy for hepatitis B virus (HBV)-related HCC.
Method: This historical cohort study included 1,695 consecutive patients who were treated with entecavir (n = 813) or TDF (n = 882) after curative hepatectomy for HBV-related HCC of BCLC stage 0 or A in Korea between 2010 and 2018. Recurrence-free and overall survival were compared between entecavir and tenofovir groups by propensity score (PS)-matched and multivariable-adjusted Cox regression analyses.



Results: Of the study patients, mean age was 54.8 years and 1,294 patients (76.3%) were male. Median duration of follow-up was 37.6 months. Compared with entecavir, tenofovir therapy was associated with a significantly lower rate of HCC recurrence by PS-matched analysis of 567 pairs of patients (P = 0.02) and multivariable-adjusted analysis of the entire patients (hazard ratio [HR], 0.82; 95% CI, 0.68–0.98; P = 0.03; Figure). Overall mortality was also significantly lower in the tenofovir group compared with entecavir group by PS-matched analysis (P = 0.03) and multivariable analysis (HR, 0.62; 95% CI, 0.44–0.88; P = 0.01). Tenofovir therapy was an independent protective factor for both early (<2 years; HR, 0.79; 95% CI, 0.64–0.97; P = 0.03) and late (≥2 years; HR, 0.68; 95% CI, 0.47–0.97; P = 0.03) HCC recurrence.
Conclusion: Among patients who undergo curative hepatectomy for HBV-related HCC, tenofovir therapy was associated with significantly better recurrence-free and overall survival rate compared with entecavir therapy.

AS095

A prospective study of nucleot(s)ide analogue discontinuation in non-cirrhotic HBeAg-negative chronic hepatitis B patients: interim analysis at week 48 demonstrates profound reductions of HBsAg associated with ALT flare

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Background and Aims: Current guidelines recommend indefinite Nucleot(s)ide Analogue (NA) therapy for patients with HBeAg-negative CHB. However, sustained virological response (SVR) has been described in patients after discontinuation of long-term NA therapy, as well as HBsAg loss. The HBV-STOP study is a prospective multi-centre study of NA discontinuation in patients who have achieved long-term virological suppression on treatment. The study describes clinical outcomes post-treatment discontinuation, with the aim of identifying determinants of SVR.
Method: An interim narrative analysis of outcomes at week 48 post-NA discontinuation was performed. The primary endpoint for the study is outcomes at week 96. Inclusion criteria for the study were HBeAg-negative, non-cirrhotic & virological suppression for ≥18 months on NA therapy uninterrupted for ≥2 years. Criteria for recommencing NA therapy were HBV DNA >2000 IU/mL with either ALT >5× ULN for ≥16 weeks or ALT >10× ULN for ≥8 weeks, INR ≥1.5, Bilirubin >2× ULN, ascites, hepatic encephalopathy and investigator discretion.
Results: The cohort is fully enrolled and data are currently available for 90/111 patients. At baseline, median age was 55 yrs, 58% were male, 83% were Asian. Median HBsAg level was 699 (250–1819) IU/mL. All patients were non-cirrhotic. Virological reactivation occurred in all, with median time to detection 8 (4–12) weeks. At week 48, four (4%) patients have experienced HBsAg loss, 42 (47%) had DNA <2,000 IU/mL, 13 (14%) had DNA >2,000 and ALT >2× ULN, and 10 (11%) had restarted treatment. Patients who achieved HBsAg loss had low baseline HBsAg levels (HBsAg loss: median baseline HBsAg level = 3.1 IU/ml in HBsAg loss vs. 776 IU/mL in patients with no HBsAg loss). The overall median reduction in HBsAg was 68 IU/mL at week 48. 21 (23%) have experienced an ALT flare >10× ULN. ALT flare was associated with reduction in HBsAg level. Median reduction of HBsAg level from the flare time-point to week 48 was 2800

(106–6090) IU/mL (vs 41.7 IU/mL in patients with peak ALT <10× ULN, p-value =<0.001).
Conclusion: In this interim analysis, stopping NA therapy was associated with virological relapse, but at week 48 only 11% had restarted NA therapy. ALT flare >10xULN was observed in 23% and was associated with profound reductions in HBsAg levels, suggesting that immunological flare may be important for achieving HBsAg loss. HBsAg loss itself was observed in a minority at week 48.

AS169
High HBsAb titers consistent across 3 lots of the trivalent HepB vaccine, Sci-B-Vac: Results from the second pivotal phase 3 double-blind, randomized controlled trial designed to assess the lot-to-lot consistency of Sci-B-Vac in adults (CONSTANT)

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Background and aims: Hepatitis B Virus (HBV) infection remains a significant and rising global public health concern, one for which vaccination is a critical measure to prevent transmission. Sci-B-Vac® is a trivalent HepB vaccine (TV), containing S, pre-S1, and pre-S2 antigens, that has shown enhanced seroprotection rates (SPR) in adult populations when compared to monovalent vaccines (MV), such as Engerix-B®.
Method: In a double-blind 4-arm study (NCT03408730), the consistency of immune response elicited by vaccination with TV (at Days 0, 28, and 168) from 3 separate lots (A, B, C) was assessed, and the pooled immunogenicity of TV was compared to MV. Participants were randomized across 32 clinical study sites in USA, Europe, and Canada. The primary endpoint was manufacturing equivalence of 3 consecutive lots of TV, defined as the 95% confidence intervals (CI) of each pairwise comparison of the ratios of geometric mean concentration (GMC) of Hepatitis B antibodies (HBsAb) being between 0.67 and 1.5. The secondary objectives included (1) demonstration of non-inferiority of SPR, defined as % participants with anti-HBsAg titers ≥ 10 mIU/mL, of TV vs. MV and (2) safety and tolerability, including solicited adverse events (AEs) within 7 days and unsolicited AEs within 28-days after vaccination, serious AEs (SAEs), medically-attended events or new onset of chronic illness (NOCI) to end of study, at least 24 weeks after the third dose of vaccine.
Results: 2,838 participants, age 18-45 years, were randomized across 4 arms – MV (n=712), TV Lots A (n=711), B (n=709) and C (n=706). The primary objective of lot-to-lot manufacturing consistency was met, with each pairwise comparison falling within the pre-defined 95% CI intervals for the GMC ratios, A & B [0.67, 1.00], B & C [0.95, 1.41], A & C [0.78, 1.15]. Compared to MV, the pooled antibody GMC achieved with TV was >7.5x after 2 vaccinations and >3x after 3 vaccinations (Fig. A). The secondary objective — SPR of the pooled TV was non-inferior to MV and was also higher than MV after both two (90.4% vs. 51.5%) and three (99.3% vs. 94.8%) vaccinations (Fig. B). Slightly higher pain and tenderness rates were noted with TV. Unsolicited and medically-attended AEs were well-balanced; the number of SAEs (<2.5%) and NOCIs (≤1.6%) were low in both treatment arms.
Conclusion: TV met both the primary and secondary endpoints of the study. In this second pivotal Phase 3 study, TV continued to demonstrate its ability to safely and quickly elicit robust immune responses in adults.

Figure A:

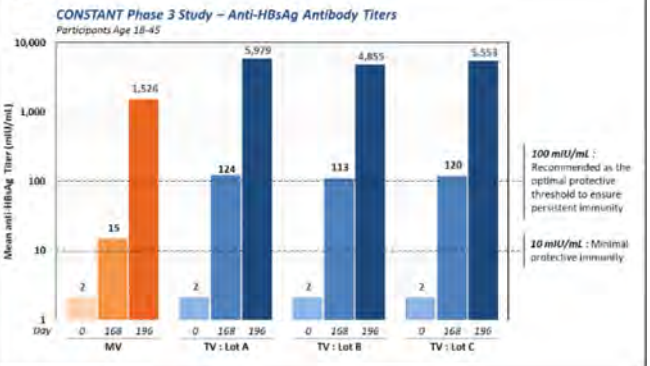
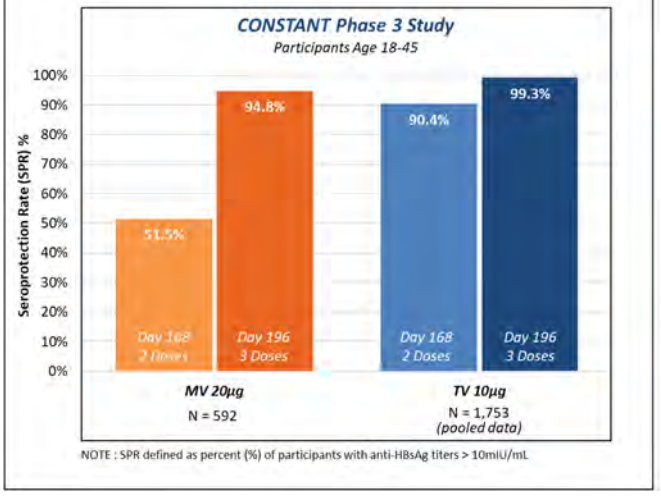


Figure B:



NAFLD – Non invasive assessment

AS096
Repeated measures of FIB-4 improve prediction of severe liver disease: population-based cohort study of 40,729 individuals

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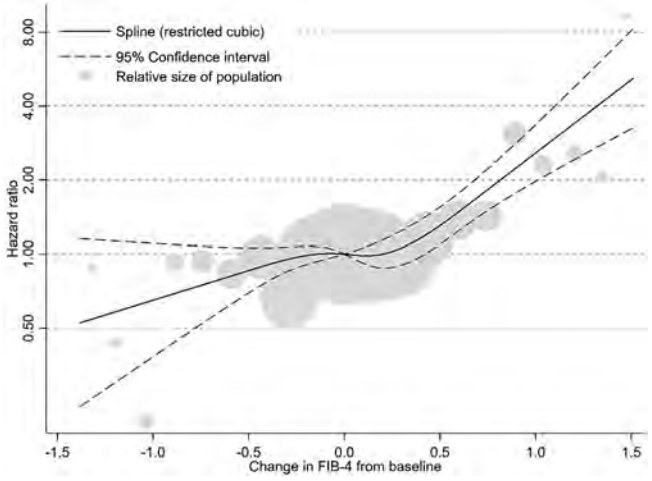
Background and Aims: Non-invasive scores to detect advanced liver fibrosis are commonly used and can to some extent also detect future liver-related events. There is limited data on if repeated

measurements can improve prediction, especially in a general population or primary care setting.
Method: We used data from the population-based AMORIS cohort in Stockholm, Sweden (N > 800,000 examined 1985–1996). Persons with liver diseases other than NAFLD were excluded. We calculated the commonly used FIB-4 index in those with available data at two separate times within five years, and associated changes in FIB-4 as well as transitions between low/intermediate/high-risk groups with outcomes. For those with multiple measurements, the first and last measurements were used. Incident severe liver disease was ascertained after the second measurement. This was a composite outcome that included diagnoses of cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and death in liver disease, ascertained though linkage with national registers until the end of 2011. Cox regression models adjusted for age, sex, socio-economy and time between measurements were applied to obtain hazard ratios (HR).
Results: Of 126,942 persons with available FIB-4 data, 40,729 (32.1%) had a repeated measurement of FIB-4 within 5 years. Median FIB-4 increased from 0.91 (IQR 0.67–1.24) to 0.96 (IQR 0.69–1.29), or 0.02 per year. During >613,000 person-years of follow-up, there were 581 events of severe liver disease (1.4%). An increase of one unit in FIB-4 was associated with an increased risk of severe liver disease (aHR 1.81, 95%CI 1.67–1.96). Transitioning from low/intermediate risk groups to high risk groups were also associated with increased risk compared to those at consistent low risk (aHR 7.99 and 8.64 respectively). A particularly increased risk was found in persons defined as high-risk at both testing occasions (aHR 17.04, 95%CI 11.67–24.88). However, almost half of the 581 events occurred in persons that were in the low risk group at both testing occasions. A restricted cubic spline graph on the risk of severe liver disease by change in FIB-4 is presented in Fig. 1.



Conclusion: These results suggest that repeated testing of FIB-4 within five years improves prediction of incident cirrhosis or complications thereof, but that currently used risk assessment tools need to be improved.

AS097

Utility of magnetic resonance elastography in accurate identification of candidates for pharmacologic treatment of NASH related fibrosis: a prospective cohort study

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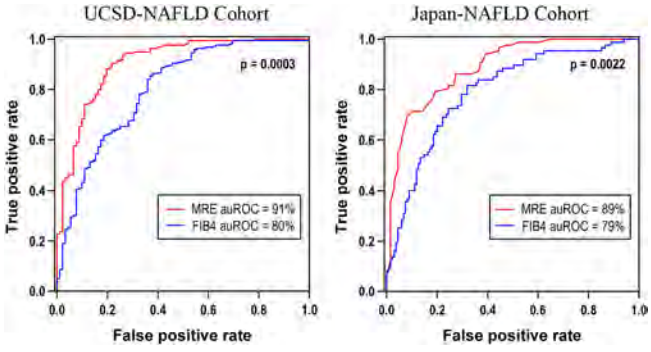
Background and Aims: Patients with non-alcoholic fatty liver disease (NAFLD) with stage 2 fibrosis or higher are at increased risk for liver related mortality and are candidates for pharmacologic therapies for treatment of NAFLD. However, there is paucity of data on utility of non-invasive biomarkers for identifying patients who are candidates for treatment in registrational trials without a liver biopsy. The aim of this prospective study was to examine the diagnostic accuracy of magnetic resonance elastography (MRE) in well-characterized patients with biopsy-proven NAFLD and then validate these findings in an external validation cohort.
Method: This is a *cross-sectional* analysis of a *prospective cohort* (UCSD-NAFLD) including 311 consecutive patients with biopsy-proven NAFLD and contemporaneous MRE. Patients underwent standardized research visit including history, physical examination, laboratory analysis, MRE, and liver biopsy using NASH-CRN-Histologic Scoring System. The radiologist and pathologist were blinded to clinical, pathological, and imaging data respectively. Receiver operating characteristics were determined to examine the diagnostic accuracy of MRE for diagnosis of ≥ stage 2 fibrosis in NAFLD. We then validated these findings in an independent validation cohort derived from Yokohama University in Japan (Japan-NAFLD) Cohort.
Results: The mean (±SD) age and BMI of the UCSD-NAFLD Cohort was 50.9 (±13.6) years and 31.6 (±5.9) kg/m^2, and the Japan-NAFLD Cohort was 55.5 (±15.1) years and 28.8 (±5.1) kg/m^2, respectively. In the UCSD-NAFLD (training) Cohort, MRE demonstrated a robust and clinically significant diagnostic accuracy for the detection of ≥ stage 2 fibrosis with an AUROC of 0.91 (95% CI: 0.87–0.94) versus FIB-4 alone with an AUROC of 0.80 (95% CI: 0.75–0.86), which was both clinically and statistically significant ($p < 0.0005$). The diagnostic accuracy of MRE remained statistically significant in the Japan-NAFLD (validation) Cohort with an AUROC of 0.89 (95% CI, 0.85–0.93, $p < 0.0001$). We then combined MRE with FIB-4 (MRE ≥ 3.2 kPa and FIB-4 ≥ 1.5) to develop a clinical prediction rule to rule in ≥ stage 2 fibrosis patients which had positive predictive value (PPV) of 89.5% in the UCSD-NAFLD Cohort [MRE ≥ 3.2 kPa adjusted OR: 22.88 (11.47–45.66), and FIB-4 ≥ 1.5 adjusted OR 4.7 (2.33–9.47); p-value <0.0015] and remained significant at 89.7% in the Japan-NAFLD Cohort (p-value <0.002).



Conclusion: MRE coupled with FIB-4 may be used for non-invasive identification of candidates for (≥ stage 2 fibrosis) pharmacologic therapy among patients with NAFLD.

AS098

Machine learning outperforms existing non-invasive tests as screening tool for liver fibrosis in the general population

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Background: Risk stratification is key to reduce unnecessary testing in liver disease screening. While transient elastography (TE) could be considered the non-invasive gold standard for liver fibrosis diagnosis, evidence regarding which features or scoring systems help to discriminate at-risk patients in the general population is built upon heterogeneous and small studies. Therefore we aimed to evaluate which risk factors better predict elevated TE values by means of using supervised learning models.

Patients and Methods: Data from six prospective cohorts (5 Europe, 1 Hong Kong) from the general population who underwent screening for liver fibrosis with TE was included. In total, 32 variables, including demographics, biometrics, and analytical parameters, were used in training a diagonal discriminant analysis model. TE values above 9.1 kPa were considered positive cases for significant liver fibrosis (≥F2). A SMOTE sampling algorithm was used to balance positive/negative cases. Missing values were imputed by means of multiple imputation forests. Internal validation was accomplished via 5-fold cross-validation. Discriminatory accuracy, measured as area under the ROC curves, of the final model was compared to the one of univariate traditional risk factors.

Results: The analysis included 6,199 patients(mean age 54.7 yrs, sd 12.2, 52% women, mean LSM 5.6 kPa, sd 5) with 5,856 negative and 343 positive cases. The final machine learning (ML) model, with 32 variables, presented AUC of 0.88(95%CI: 0.87–0.9). Analyzing individual variables, we detected that AUC for abdominal perimeter was 0.71(0.68–0.74), AST 0.73(0.70–0.76), and albumin 0.68(0.64–0.71). The ML model had higher accuracy than FIB-4 score or NFS in our population [AUC 0.88(0.86–0.90) for ML, 0.68(0.65–0.71) for FIB-4, 0.71(0.68–0.74) for NFS]. If a different ML model was constructed using a cutoff value of TE of 14 kPa, suggestive of cirrhosis, the accuracy of the model was 0.95 (0.94–0.97), compared to 0.79(0.75–0.83) and 0.78(0.74–0.82) for FIB-4 and NFS, respectively.

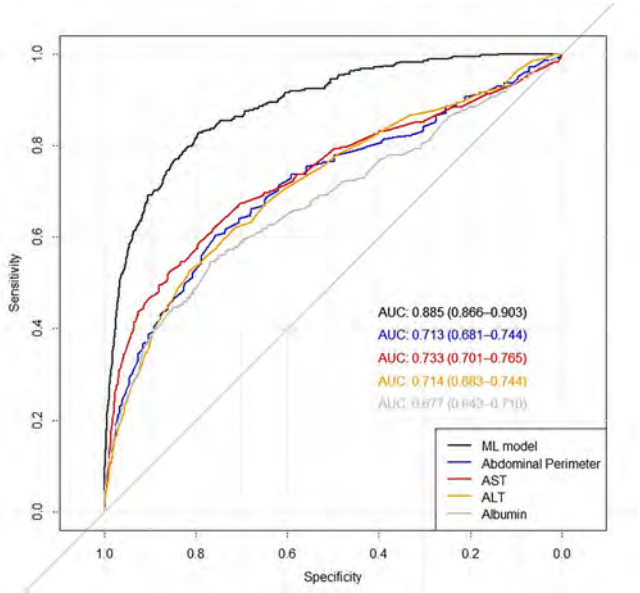

Figure: ROC curves of final ML model vs individual risk factors.

Conclusions: The ability to predict pre-test individual risk of liver fibrosis may prove useful as a mean of reducing unnecessary testing. Our results suggest that pre-test risk stratification is feasible and accurate with routine check-up data. Moreover, abdominal perimeter alone might have similar predictive value than common liver function serologic markers, highlighting its potential usefulness in settings with limited resources.

AS100

Progression of liver stiffness and the development of cirrhosis in histologically characterized patients with non-alcoholic fatty liver disease

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Background and Aims: Vibration Controlled Transient Elastography (VCTE) is widely used for assessing the presence and progression of liver stiffness (LS), a surrogate for liver fibrosis, in patients (pts) with nonalcoholic fatty liver disease (NAFLD). However, the natural history of LS in pts with NAFLD is not well understood. Our aims were to characterize 1) longitudinal changes in LS stratified per baseline histological fibrosis stage and 2) time to and factors associated with developing LS defined cirrhosis (LSM >14.9 kPa) in pts without cirrhosis on initial VCTE.

Method: VCTE was performed annually per protocol starting in 2014 in the NASH CRN Database 2 study, which enrolled and prospectively followed pts with biopsy-proven NAFLD from 2009 to 2019. Random effects models were used for estimation of change in LS over time and Kaplan-Meier with staggered entry methods for time-to-event statistics; stepwise Cox regression was used for risk factor analysis selecting from a candidate set of 22 clinical, anthropometrics, histological, and laboratory variables at first VCTE visit.

Results: We studied 1,010 individuals (mean age 51 years, 63% women, and 86% Caucasian), of whom 58% had definite NASH and 8% had cirrhosis on biopsy. The number of serial VCTEs performed were 2 in 289, 3 in 246, 4 in 272 and ≥ 5 in 203 pts. The LS increased significantly over time only in pts with baseline stage 3 liver fibrosis

(0.57 (95% CI: 0.22, 0.93) kPa/year, p = 0.001) but not in pts with other liver fibrosis stages (Table). In pts without cirrhosis by LS at first VCTE visit, the annual risk of developing cirrhosis by LS criteria was 6.8% and the 25th percentile time to developing LS defined cirrhosis was 4.4 years (95% CI: 1.3–6.0 years). Risk factors associated with progression to cirrhosis were: increasing waist circumference per cm (HR 1.01, 95% CI: 1.00–1.02), increasing platelet count per 1 K/mm^3 (HR: 0.995, 95% CI: 0.992–0.998), higher portal inflammation by each point (HR: 1.5, 95% CI: 1.0–2.2), higher fibrosis by one stage (HR: 1.7, 95% CI: 1.4–2.0), higher INR by 0.1 (HR 3.3, 95% CI: 1.0–10.6), lobular inflammation by each point (HR: 0.8, 95% CI: 0.6–1.0), and higher GGT per U/L (HR: 1.003, 95% CI: 1.000–1.006).

Baseline liver histological fibrosis	Number of pts	Total Number of VCTE	Median (IQR) Years of Follow-up	Annual change in LS (95% CI)	P-value
F0	254	850	2.6 (1.7, 3.4)	0.16 (−0.02, 0.33)	0.08
F1	253	855	2.6 (1.7, 3.3)	−0.01 (−0.18, 0.16)	0.93
F2	185	633	2.7 (1.9, 3.4)	0.14 (−0.12, 0.39)	0.30
F3	**231**	**801**	**2.8 (1.8, 3.4)**	**0.57 (0.22, 0.93)**	**0.001**
F4	85	277	2.5 (1.3, 3.2)	0.45 (−0.40, 1.31)	0.30

Conclusion: In a cohort of NAFLD pts enriched with NASH, the annual risk of cirrhosis by LS criteria was ~ 7%. LS significantly worsened only in those with stage 3 fibrosis on baseline liver biopsy. These observations might be useful in clinical practice and for designing early phase clinical trials with noninvasive endpoints.

AS101

Convolutional neural networks of H&E -stained biopsy images accurately quantify histologic features of non-alcoholic steatohepatitis

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Background and Aims: Current staging systems for NASH have limited utility for quantitative analyses due to their low resolution and ordinal nature. To address these limitations, we trained convolutional neural networks (CNNs) to produce continuous scores for key NASH features from biopsy images and assessed the explanatory power of these models to predict NASH-related biomarkers as compared to pathologist-derived scores.
Method: We analyzed 4,641 whole-slide images of H&E-stained biopsies from five NASH clinical trials evaluating simtuzumab and selonsertib. All biopsies were evaluated by a central pathologist (CP) according to the NASH CRN and Ishak classifications. Based on CP readings, we trained end-to-end deep CNNs to predict scores for steatosis, lobular inflammation, ballooning, and fibrosis. These models extract histological features for multiple tiles (192 × 192 μM) of a single slide and integrate them to predict biopsy-level CP scores. The model incorporated an attention mechanism to weight the importance of tiles used for predictions, which permitted identification of informative tiles without explicit supervision. We used 90% of the slides for training and validation, and the remaining 10% to evaluate the agreement between the CNN-derived and CP scores (Spearman ρ; test slides from different patients and sites). The ability of the histological scores to predict 60 NASH-related serum markers was examined using linear regression models adjusted for age, sex, BMI, and treatment. Out-of-sample predictive performance was assessed using Spearman correlation between predicted and true values.
Results: In the test set, the CNN-derived scores were highly correlated with those of the CP for Ishak stage (ρ = 0.90), steatosis (ρ = 0.70), ballooning (ρ = 0.71), and lobular inflammation (ρ = 0.67; all $p < 10^{-50}$). Agreement did not differ in a sensitivity analysis based on the number of evaluated tiles. Despite the model being trained on biopsy-level scores, the attention mechanism weighted tiles with features that align with those used by a pathologist (Fig. A). Notably, the weighting of tiles for each histological score was different for steatosis, lobular inflammation, and fibrosis (Fig. B-C). Compared with CP-derived scores, the CNN-derived scores had improved prediction accuracy for most NASH biomarkers, with significant improvements for ELF, TIMP-1, PIII-NP, α_2-macroglobulin, insulin, HOMA-IR, and monocyte/leukocyte ratio (Δρ = 0.08–0.15; Bonferroni-adjusted p < 0.05).

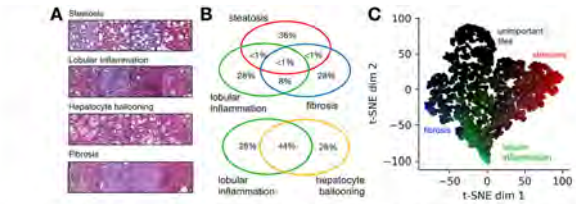

Figure | Results from the convolutional neural network (CNN) approach. (A) Example of tiles with high importance weights for steatosis, lobular inflammation, hepatocyte ballooning and fibrosis. **(B)** Venn diagrams showing the overlap among the sets of the top 10% of the tiles for each score. We observed a high overlap for lobular inflammation and hepatocyte ballooning. **(C)** t-SNE map of tile-level histological features extracted from our model for 10,000 randomly selected tiles. Tiles with high importance weights for steatosis, lobular inflammation and fibrosis are colored in red, green and blue, respectively. Hepatocyte ballooning has been omitted given the overlap with lobular inflammation.

Conclusion: CNNs trained on whole slide liver biopsy images can be utilized to extract continuous scores that recapitulate the key histologic features of NASH. These scores show improved correlations with multiple biomarkers of NASH severity, and represent a novel strategy for quantitative histological analysis and association studies with other data types.

AS102

Serum levels of miR-34a to rule-out NAFLD in healthy subjects and identify NAFLD patients with active NASH (NAS>= 4) and significant liver fibrosis (F >= 2)

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Background and Aims: MiR-34a has been proposed as a biomarker for NASH. The aim was three fold: i) to assess the potential of circulating levels miR-34a to eliminate healthy subjects from those with liver disease, ii) to cross-validate diagnostic performance of miR-34a in independent cohorts to be able to identify patients with NASH (NAS ≥ 4) and fibrosis (F ≥ 2) (i.e. NAS ≥ 4+F ≥ 2), who are at higher risk of liver-related outcomes, and iii) to compare miR-34a with other blood-based biomarkers and scores.
Method: MiR-34a was measured by RT-qPCR in serum samples from 100 blood donors considered as healthy subjects and from 1,214 patients with a liver biopsy because of suspicion of NAFLD. Patient data was derived from 4 independent cohorts: GOLDEN-505 (N = 264), RESOLVE-IT (N = 484), Angers (N = 228) and Antwerp (N = 238). Liver biopsies, NAFLD activity score (NAS) and fibrosis stage were evaluated using NASH-CRN scoring systems and were centrally read

by expert pathologists. Diagnostic performance of miR-34a and other blood tests were assessed by AUROC and comparative statistics were done by De Long test.
Results: Blood donors had 4-fold lower levels of miR-34a as compared to patients with NAFLD (Cq = 33.95 ± 0.56 vs 31.97 ± 1.15, p < 0.0001). Among patients with NAFLD, miR-34a levels in NAFL were 2-fold lower than in patients with NASH (Cq = 32.79 ± 1.01 vs 31.84 ± 1.11, p < 0.0001). Thus, miR-34a is a robust biomarker to discriminate healthy subjects from patients with NAFLD (AUC = 0.94), NAFL (AUC = 0.85) or NASH (AUC = 0.96). In all patients, levels of miR-34 increased with NAS and fibrosis stage (p < 0.0001). MiR-34a showed similar performance to identify patients with NAS ≥ 4+F ≥ 2: AUCs were 0.73 in GOLDEN, 0.79 in RESOLVE-IT, 0.77 in Angers, 0.79 in Antwerp. In the meta-cohort (N = 1,214), miR-34a levels were higher in patients with NAS ≥ 4+F ≥ 2 vs NAS<4/F < 2 (Cq = 31.38 ± 1.02 vs 32.55 ± 1.02, p < 0.0001) with an AUC = 0.80. In head-to-head comparisons, miR-34a outperformed all other single biomarkers for NASH and fibrosis (ALT, AST, CK18-M30 and M65, A2M, TIMP1 or hyaluronic acid) and composite scores FIB4, NFS or ELF.
Conclusion: MiR-34a is a reliable biomarker that can efficiently rule-out NAFLD in healthy subjects. In patients with suspicion of NAFLD, miR-34a can be a significant contributor towards the identification of NAS ≥ 4+F ≥ 2 in patients with suspected disease. This study further supports the use of miR-34a-based candidate diagnostic test score NIS4 to screen populations with risk factors for NASH.

Portal Hypertension

AS103

Early-tips should be performed in high-risk cirrhotic patients despite the presence of hepatic encephalopathy at admission

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Background and Aims: Baveno VI recommendations state that early transjugular intrahepatic portosystemic shunt (TIPS) must be considered in high-risk cirrhotic patients (pts) with acute variceal bleeding (AVB), i.e pts with child-Pugh B cirrhosis and active bleeding or with Child-Pugh C10–13. Despite this, recent real-life studies point out that less than 10% of pts eligible for early-TIPS effectively undergo TIPS, mainly because of the fear of hepatic encephalopathy (HE) development after TIPS, especially in pts presenting HE at admission. The aims of this study were: (1) to assess the prevalence of HE at admission in pts with AVB; (2) to evaluate the outcome of pts presenting HE at admission after early-TIPS placement; (3) to determine if HE at admission was an independent factor of death and further development of HE.
Method: Multicenter, international, real-life observational study including 2138 pts from 34 centers between April 2013 and April 2015. Pts were managed according to current guidelines. Placement of TIPS in high-risk pts was based on individual centre policy. Exclusion criteria were: age>75, pregnancy, hepatocellular carcinoma outside the Milan criteria, a creatinine level>265 μmol/L, a Child–Pugh score>13, active sepsis, heart failure and total portal-vein thrombosis; pts were followed up to 1 year, death, or liver transplantation.
Results: 1521 pts met inclusion criteria and were analysed (age 56 ± 11 yrs, male gender 75%, Child-Pugh A/B/C = 49/29/22%, MELD score 21 ± 7). Among them, 671 were considered at high-risk, 66 received early-TIPS and 605 endoscopic +drug treatment. At admission, HE was significantly more frequent in high-risk than in low-risk pts (38.1% vs 10.6%, p = 0.008). In high-risk pts with HE at admission, early-TIPS placement was associated with a significantly better survival than endoscopic + drug treatment (HR 0.453 [0.218–0.940], p = 0.03), even in the subgroup of Child-Pugh C pts (HR 0.419 [0.203–0.868], p = 0.02). In pts without HE at admission, the occurrence of HE during follow-up was not different between pts who underwent early-TIPS vs endoscopic + drug treatment (16.7% vs 17.6%, p = 0.86). Recurrent HE was less frequent in pts with HE at admission treated with early-TIPS than in those receiving endoscopic + drug treatment (16.7 vs 27.3%, p = 0.04). In multivariate analysis, age, the presence of shock, a MELD score>15, endoscopic + drug treatment and HE at admission were independent factors predicting death in high-risk pts.
Conclusion: HE at admission is independently associated with poor survival in high-risk pts with AVB. In the subgroup of high-risk pts with HE at admission, early-TIPS significantly improved survival, recovery of HE and decreased the occurrence of new HE episodes after AVB. There is no rationale for the fear of early TIPS in pts with AVB and HE at admission.

AS104

Endoscopic cyanoacrylate injection versus balloon-occluded retrograde transvenous obliteration as secondary prophylaxis of gastric variceal bleeding: a prospective randomized controlled trial

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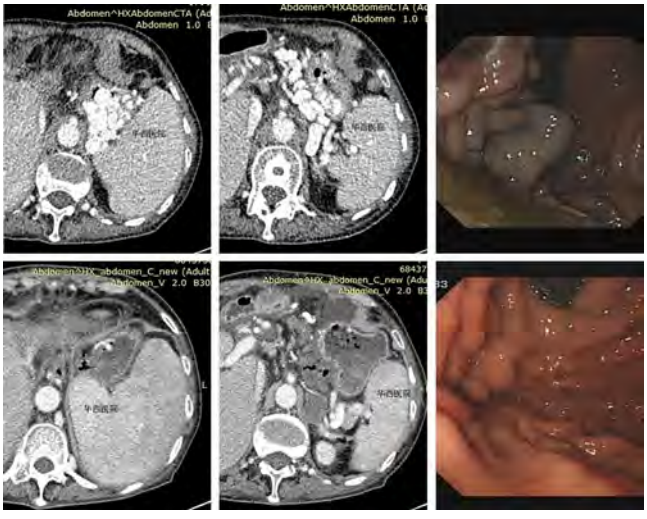
Background and Aims: It is generally considered that gastric varices (GVs) bleed less frequently than esophageal varices (EVs); however, rupture of GVs are associated with more severe hemorrhage and higher mortality. The evidence to support recommendations for the management of GVs rebleeding is much less robust than that for EVs. The optimal treatment of GVs has not fully been determined. The current study aimed to compare the efficacy and safety of endoscopically cyanoacrylate injection and balloon-occluded retrograde transvenous obliteration (BRTO) in the prevention of rebleeding in patients with GVs after primary hemostasis.
Method: Between June 2015 and Feb 2018, 64 patients with previous GOV2 or IGV1 bleeding were randomly assigned either cyanoacrylate injection (n = 32) or BRTO (n = 32). Primary outcomes were gastric variceal rebleeding and all-cause bleeding.
Results: The mean follow-up time was 27.1 ± 12 months in the cyanoacrylate injection group and 27.6 ± 14.3 months in the BRTO group. The technical success rate was 96.9% in the BRTO group. The amount of polidocanol was 12.5 ± 4.5 ml. Complete obliteration rate of GVs was higher in the BRTO group (96.9% vs. 81.3%). 11 patients in the cyanoacrylate injection group and 2 patients in the BRTO group rebled. The most common bleeding source was GVs or glue injection-related ulcer. The 1-year and 2-year cumulative probability of remaining free of GV rebleeding and all-cause rebleeding was significantly higher in the BRTO group than in the cyanoacrylate group. The cumulative survival rates at 1 and 2 years for cyanoacrylate injection versus BRTO were 90.6% versus 93.8% and 87% versus 86.2%, respectively. There was no difference in aggravation of EVs. The mean number of hospitalizations, days in hospital and overall charges of hospitalization were also higher in the cyanoacrylate injection group.



Conclusion: The results of our study clearly show that BRTO is remarkably more effective than cyanoacrylate injection in the prevention of rebleeding from GVs, with similar frequencies of complications and mortalities. Therefore, BRTO could be recommended as the first choice for secondary prevention in patients with fundal GVs when technically applicable.

AS105

A multicenter analysis of the role of prophylactic transfusion of blood products in patients with cirrhosis and esophageal varices undergoing endoscopic band ligation

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Background and Aims: Prophylactic administration of platelets and fresh frozen plasma (FFP) is commonly recommended in patients with cirrhosis with low platelets and/or prolonged INR without scientific evidence to support this practice. In this analysis we evaluated the use of prophylactic administration of blood products in outpatients with cirrhosis undergoing endoscopic band ligation (EBL).
Methods: This is a multicenter retrospective analysis of consecutive EBL procedures in patients with cirrhosis at 4 hospitals in Spain (Hospital Clinic, Barcelona Hospital Universitari Mutua de Terrassa, Consorci Sanitari de Terrassa and Corporació Sanitària Parc Taulí) from 01/2010-01/2017. FFP and/or platelet transfusion were administered at the discretion of the physician if INR was >1.5 and/or platelet count $<50 \times 10^9$/L. Patient demographics, endoscopic findings, bleeding events after EBL, and the use of prophylactic FPP or platelets were recorded.
Results: 536 patients underwent 1472 EBL procedures: (72% male), the main etiology was HCV and alcohol (72%), median MELD 11, Child A/B/C (59/33/8%). EBL procedures were performed for primary (51%) or secondary (49%) prophylaxis. Median procedure per patient was 2 (1–4). The prophylactic transfusion protocol was followed in 12.5% and 32.4% of procedures with high INR and/or low platelets respectively. FPP and/or platelets were administered in 37 patients (6.9%). Post EBL-bleeding occurred in 26 patients out of 1472 procedures (1.7%). Bleeding was due to post-EBL ulcers in 21 patients and due to band dislodgment in 5. In six patients, bleeding occurred within 24 hrs and in the remaining it occurred within 2 weeks after EBL. In those that bled, 7 met criteria for transfusion (2 for FFP and 5 for platelets); of these only 1 received FPP and 3 platelet transfusion; the remaining 19 patients did not meet criteria for transfusion. There was no association between INR or platelet count and bleeding events. Patients that bled had higher Child and MELD scores compared to those that did not bleed (p = 0.03 and p = 0.02, respectively).
Conclusion: The incidence of post EBL bleeding is <2% and is associated with advanced liver disease. There was no relationship between post-EBL bleeding and the baseline INR/platelet count before the procedure. In addition, the majority of outpatients with post-EBL bleeding did not meet criteria for the standard prophylactic transfusion policy.

AS106

Anticoagulation and transjungular intrahepatic portosystemic shunt for the management of portal vein thrombosis in cirrhosis: a prospective observational study

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Background and Aims: Limited data are available on the management algorithm for portal vein thrombosis (PVT) in cirrhosis. The study aimed to prospectively evaluate anticoagulation and transjugular intrahepatic portosystemic shunt (TIPS) to treat PVT.
Method: Between February 2014 and June 2018, 396 consecutive cirrhotic patients with non-malignant PVT were prospectively included in a tertiary-care center. Covered TIPS with (before 2017.05) or without (after 2017.05) post-TIPS anticoagulation was indicated in those with symptomatic portal hypertension (variceal bleeding in the past 6 weeks or refractory ascites). Anticoagulation along were indicated in those without symptomatic portal hypertension but with PVT >50% of the lumen or extended to superior mesenteric vein (SMV). Patients without symptomatic portal hypertension and PVT<50% and no SMV extension were not anticoagulated nor received TIPS. Primary endpoint was portal vein recanalization.
Results: Per the management algorithm, TIPS, anticoagulation, and un-treatment were indicated in patients 324 patients, 54 patients and 18 patients, respectively. TIPS was successfully placed in 285 of 324 patients (88.0%), of which 197 patients was anticoagulated after TIPS while 88 patients was not anticoagulated. Among the 39 patients who failed TIPS, 9 patients received anticoagulation and 30 patients were not treated. Finally, 197 patients (49.8%) received TIPS plus post-TIPS anticoagulation (TIPS+AC group), 88 patients (29.7%) received TIPS alone (TIPS group), 63 patients (17.4%) received anticoagulation

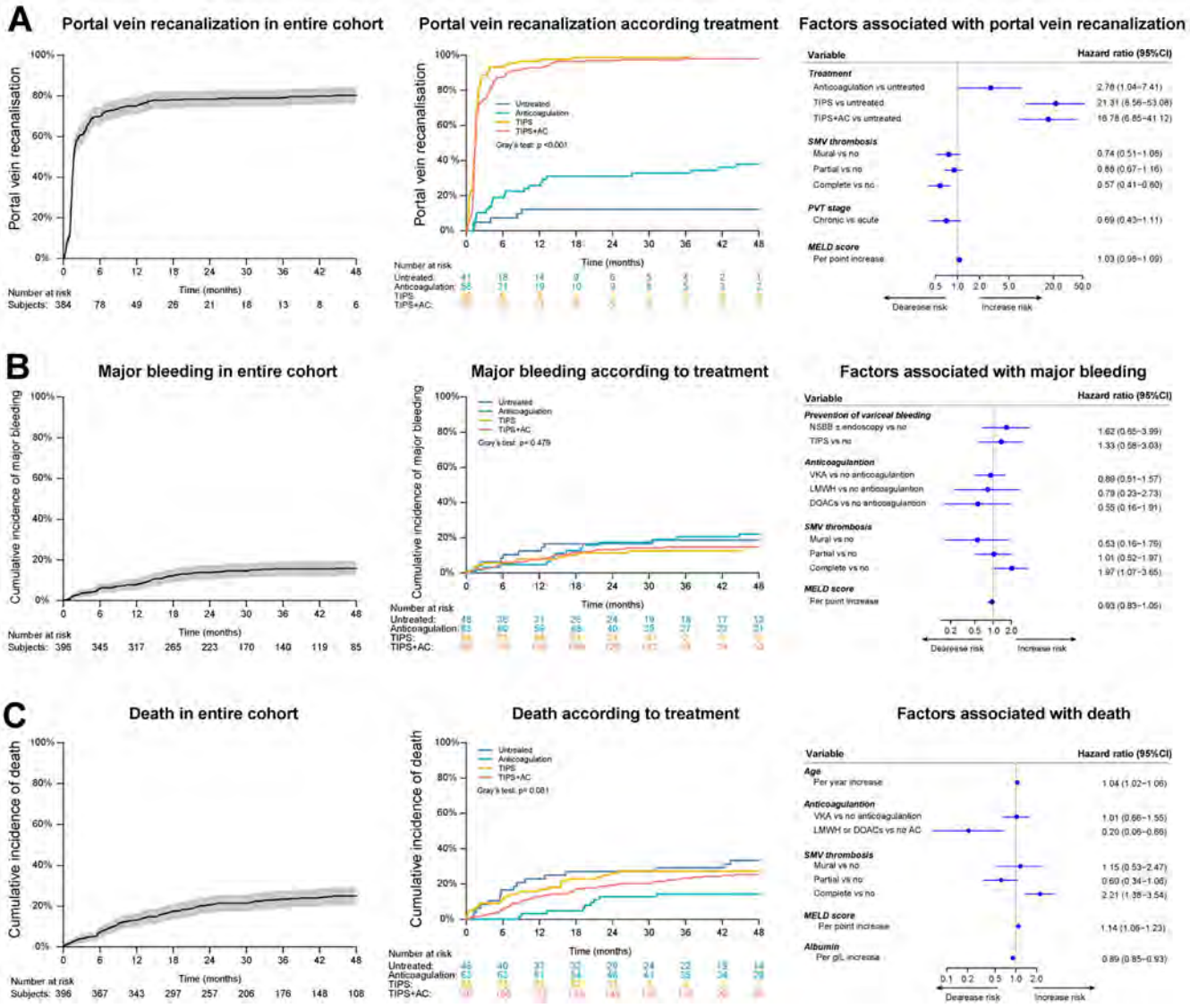

Figure: (abstract: AS106)

alone (anticoagulation group) and 48 patients (12.1%) were not treated (untreated group). Follow-up imaging studies were not available in 12 patients. In the remaining 384 patients, recanalization (partial or complete) was observed in 312 (81.3%) patients. TIPS creation and anticoagulation was associated with a higher probability of portal vein recanalization, while complete SMV thrombosis is inversely associated with recanalization (Figure A). During a median 31.7 months (IQR 18.1to 49.5) of follow-up, major bleeding (defined in accordance with the International Society of Thrombosis and Haemostasis criteria) occurred in 64 patients (16.2%, 57 variceal bleeding, 7 non-gastrointestinal bleeding) and did not differ among groups. In multivariate analysis, complete SMV thrombosis but not anticoagulation was associated with increased risk of major bleeding (Figure B). Overall, 100 patients (25.3%) died. Anticoagulation with LMWH or DOACs but not VKAs was associated improved survival while complete SMV thrombosis was associated with higher risk of death (Figure C).

Conclusion: In cirrhotic patients with PVT, a treatment algorithm using anticoagulation and TIPS achieves a high probability of portal vein recanalization, reduces portal hypertensive complications and decreases the risk of death.

AS107

Assessment of Baveno VI and expanded Baveno VI criteria for screening and follow-up of all-size esophageal varices in patients with compensated viral cirrhosis (ANRS/CO12 CirVir cohort)

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Background and Aims: In compensated cirrhosis, endoscopy can be avoided for screening of esophageal varices (EV) when Baveno VI (BVI) criteria are favorable (platelet ≥ 150 G/L and liver stiffness measurement (LSM) ≤20 kPa). Expanded Baveno VI criteria (eBVI) (favorable when platelet ≥ 110 G/L and LSM ≤25 kPa) were suggested to avoid more endoscopies. BVI criteria were previously validated for screening and follow-up of large EV in viral cirrhosis, but eBVI criteria were never validated in this indication. Moreover, a recent trial showed that beta-blockers improved prognosis in patients with viral cirrhosis and small EV. The aims of this study were: (1) to validate eBVI criteria for screening and follow-up of large EV in patients with compensated viral cirrhosis; (2) to study BVI and eBVI criteria for screening of small EV.

Method: Patients were prospectively followed-up in 35 french centers from 2006 to 2012 (CirVir cohort). Inclusion criteria: HCV/HBV infection, compensated biopsy-proven cirrhosis, endoscopy, platelet count and LSM available and interpretable. Progression of portal hypertension (PHT) was defined as the onset of EV, an increase of variceal size or PHT-related bleeding.

Results: We included 768 patients (male 69%, HCV 82%, no viral suppression 78%): 221 (25%) and 354 patients (46%) of whom had favorable BVI and eBVI criteria respectively. Among them, all-size EV were present in 16 (7%) and 42 (12%) patients and large EV in 3 (1%) and 7 (2%) patients respectively. eBVI criteria were favorable in 112/172 patients (65%) with viral suppression at baseline: 11 (10%) had small EV and none had large EV. During follow-up (median 82.3 months), endoscopy was performed in 511 patients. Progression of PHT was observed in 173 patients (34%) and was significantly associated with unfavorable eBVI criteria at baseline, no viral suppression and GGT. Overall, 21/313 patients (7%) with viral suppression during follow-up had PHT progression, which was associated in multivariate analysis with unfavorable eBVI criteria and GGT. eBVI criteria were unfavorable at the time of progression in only 60% of patients with viral suppression.

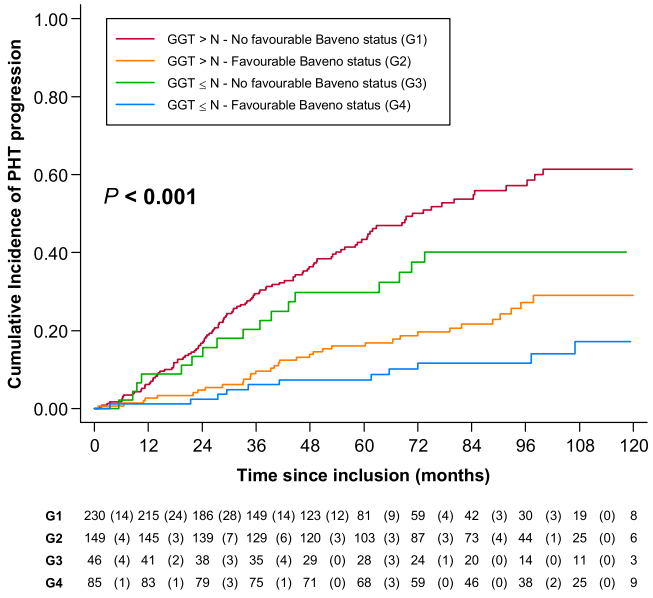

Figure: Progression of PHT was associated with unfavorable eBVI criteria and GGT.

Conclusion: eBVI criteria are sensitive enough to rule out large EV, even after viral suppression, but aren't sensitive enough to select a subgroup of patients not at risk of PHT progression. BVI and eBVI criteria aren't sensitive enough to predict small EV.

LBP29

Results of the PROFIT trial, a PROspective randomised placebo-controlled feasibility trial of Faecal mIcrobiota Transplantation in advanced cirrhosis

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Background and aims: Patients with cirrhosis exhibit dysbiotic gut microbiota, with an over-representation of pathobionts such as *Enterobacteriaceae* e.g. *E. coli*. Dysbiosis worsens with increasing severity of disease and correlates with endotoxaemia. Patients with cirrhosis are predisposed to small intestinal bacterial overgrowth and disrupted gut permeability, allowing translocation of bacteria directly into the circulation, driving systemic inflammation and disease progression. Faecal microbiota transplantation (FMT) is extremely effective in the treatment of recurrent *C. difficile* infection, with cure rates >90%. As such, interest in FMT to treat conditions linked to gut dysbiosis has grown exponentially. This is the first FMT trial undertaken in patients with advanced cirrhosis in Europe [NCT02862249].

Method: 32 patients with confirmed cirrhosis (MELD score of 10–16) consented to participate. 23 were randomised to FMT or placebo (3:1) with 21 treated (free from antibiotics for at least 14-days). After screening, patients were randomised to FMT or placebo (0.9% saline and 12.5% glycerol, without faecal material). Single donor FMT (200 ml) was prepared from six donors in a MHRA-licensed facility and administered *via* a nasojejunal tube inserted at gastroscopy (after bowel preparation with Moviprep®). Donors were rigorously screened for pathogens and samples stored for analysis in case of transmissible infection. Patients were reviewed at day 7, 30 and 90 and samples of blood, stool, urine and saliva were obtained for plasma/stool ammonia, metagenomic and metabolomic analyses.

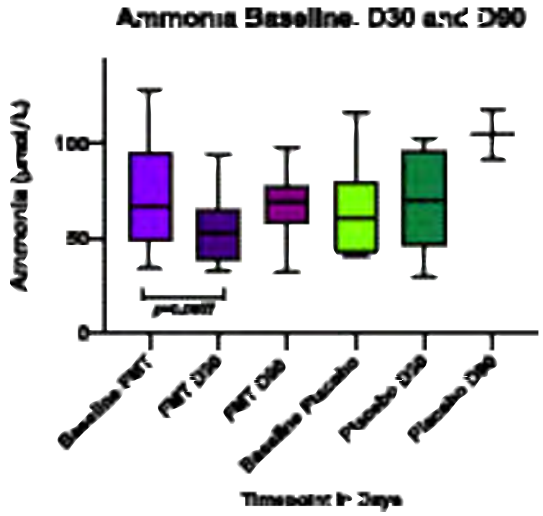

Figure: Plasma ammonia.

Results: 15 patients received FMT and 6 placebo. 76.2% of patients were male; mean age 57.8 years. The majority (52%) had alcohol-related cirrhosis (abstinent for >6-weeks). There were 10 serious adverse events (SAEs) during the follow-up period, 9 in the FMT group. None were treatment-related. There was a significant reduction in plasma ammonia between baseline and day 30 ($p = 0.0007$) and day 7 and day 30 ($p = 0.0448$), with a trend to an increase in ammonia in the placebo group. Stool ammonia levels increased in the placebo group, but not the FMT group. There were no statistically significant differences in MELD, leucocyte count and CRP.
Conclusion: FMT is safe and feasible in patients with advanced stable cirrhosis. FMT treated patients showed a striking reduction in plasma ammonia. This supports the recently published US pilot study of FMT in patients with hepatic encephalopathy.

Gut-Liver axis

AS109

Impact of global protein-tyrosine phosphatase 1b-deficiency in gut barrier function during non-alcoholic steatohepatitis

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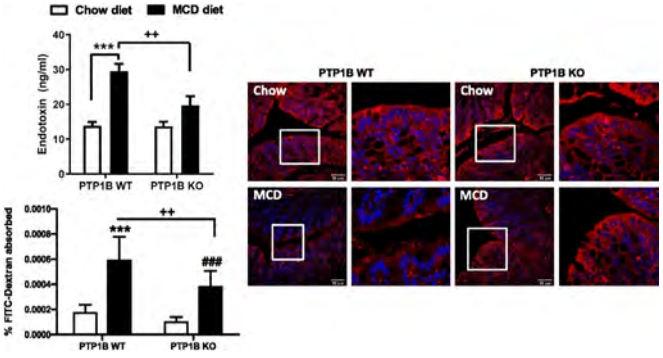
Background and Aims: Protein tyrosine phosphatase 1B (PTP1B) has been largely studied for its role as a negative regulator of the insulin receptor as well as other tyrosine kinase receptors related to inflammatory cascades. Therefore, PTP1B plays different roles in non-immune and immune cells, in the latter inhibiting pro-inflammatory signaling. Non-alcoholic steatohepatitis (NASH) is associated with a strong pro-inflammatory response at both hepatic and systemic level also concurring with a specific gut microbiome signature. In this work we aimed to decipher the role of PTP1B in the gut-to- liver axis in a preclinical model of NASH induced by methionine/choline-deficient (MCD) diet.
Method: Gut features and gut barrier dynamics were determined in wild-type and global PTP1B-deficient mice fed a chow or a MCD diet during 4 weeks. The effect of a pro-inflammatory environment was studied in enteroendocrine and intestinal epithelial cells. Glucagon-like peptide (GLP)-1 secretion was analyzed in primary colonic cultures and plasma from mice.



Results: We found a shift in gut microbiota shape, increased serum bile acid levels, disruption of gut barrier function and reduced GLP1 circulating levels in mice with NASH. Unexpectedly, despite the pro-inflammatory phenotype of global PTP1B-deficient mice, they presented a better gut barrier integrity. The preservation of gut barrier function in PTP1B-deficient mice is displayed in Figure 1 where better integrity of the tight junction protein ZO-1, minor permeability to FITC-dextran and lower levels of systemic endotoxemia are shown. Furthermore, these effects concurred with a protection against the drop of GLP-1 circulating levels during NASH in PTP1B-deficient mice compared to their wild-type counterparts together with increased expression in GLP-2-sensitive genes in the gut. Moreover, PTP1B inhibition in STC-1 enteroendocrine cells provoke an exacerbated pro-inflammatory signaling when these cells were challenged with a pro-inflammatory conditioned medium (CM) collected from lipopolysaccharide (LPS)-stimulated macrophages. Likewise, the pro-inflammatory CM induced GLP-1 secretion in primary colonic cultures, an effect augmented by PTP1B inhibition.
Conclusion: Altogether our results have unraveled a potential role of PTP1B in the gut-to-liver axis during NASH, probably mediated by increased sensitivity to GLPs, with potential therapeutic value.

AS110

MCJ deficiency results in gut barrier dysfunction and macrophage-elicited inflammation following ethanol consumption, facilitating alcoholic endotoxemia

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Background and Aims: Endotoxin-mediated hepatic damage plays an essential role in the pathogenesis of Alcoholic liver disease (ALD). Alcohol consumption leads to changes in the composition of the gut microbiome, the disruption of the gut barrier and increased intestinal permeability. Silencing of MCJ, an endogenous negative regulator of mitochondria complex I, and subsequent accelerated mitochondrial activity, has proved to prevent and rescue drug induced liver injury, and improve liver regeneration. This work aims to study the implication of MCJ in the pathogenesis of ALD, including the intestine, source of the alcoholic endotoxemia.

Method: 3-month-old wild-type (WT) and MCJ deficient ($MCJ^{-/-}$) mice were fed either with control liquid diet not supplemented or with added 5% ethanol for 10 days, followed by a single binge control or ethanol feeding, as in the NIAAA model. Hepatic and intestinal injury, gut permeability, junctional integrity and changes in gut microbiota were then assessed.

Results: Whole-body MCJ knockout proved to be detrimental in endotoxin-mediated hepatic damage. 85% of ethanol-fed WT mice survived compared to just 54% of ethanol-fed $MCJ^{-/-}$ mice. Although no differences were observed in both ethanol-fed WT and $MCJ^{-/-}$ livers, histological score was higher in the intestine of ethanol-fed $MCJ^{-/-}$ mice. Elevated expression of TNF and Il-1β were detected by qPCR, and IHC revealed higher levels of F4/80 in the gut of ethanol-fed $MCJ^{-/-}$ mice; suggesting that MCJ silencing causes an elevated infiltration of macrophages in the intestine, increasing the proinflammatory response. V3-V4 regions of 16S rDNA amplicon sequencing identified alterations of the gut microbiota in control-fed $MCJ^{-/-}$ mice, which are worsened after ethanol diet, indicating a dysbiosis event in ethanol-fed $MCJ^{-/-}$ mice. Lower abundance of Ruminococcaceae and higher levels of Bifidobacteriaceae were found in control-fed $MCJ^{-/-}$ mice. Higher levels of *Prevotella*, known to degrade mucin leading to gut barrier disruption, and lower abundance of Bifidobacteriaceae, Lactobacillaceae and Ruminococcaceae, which maintain mucosal barrier integrity, were identified in ethanol-fed $MCJ^{-/-}$ mice. Evaluation of intestinal permeability with FITC-labelled dextran showed higher levels in ethanol-fed $MCJ^{-/-}$ mice serum. Reduced expression of tight junction proteins detected by qPCR and IHC, confirms augmented intestinal permeability and decreased junctional integrity in ethanol-fed $MCJ^{-/-}$ mice; facilitating bacterial and microbial products translocation.

Conclusion: Enhanced mitochondrial activity, due to MCJ silencing, results in bacterial alterations, increased macrophage infiltration and augmented inflammatory response after ethanol consumption. These events induce the disruption of the gut barrier and elevated gut permeability, which facilitate alcohol endotoxemia and worsen ALD.

AS111

Effects of tips on gut microbiota and its relationship with postoperative hepatic encephalopathy

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Background and Aims: Hepatic encephalopathy (HE) is a major complication after transjugular intrahepatic portosystemic shunt (TIPS) and has been related to gut microbiota. The purpose of this study was to observe the effect of TIPS on gut microbiota and the relationship between the effect and postoperative HE.

Method: From May 2017 to August 2019, 78 consecutive patients with cirrhosis who were treated with TIPS due to portal hypertension were prospectively enrolled in a tertiary-care center. 23 patients developed HE (HE+ group) and 55 did not (HE- group) within 1 month after TIPS. We collected the fecal samples in all patients 1–3 days before and 1 month (range 31–37 days) after TIPS, microbiomes were analysed by 16S ribosomal RNA gene sequencing. A longitudinal study was performed to compared the taxa of patients between post- and pre-TIPS in this two groups respectively and the change amplitude of bacterial taxa between the two groups (relative abundance post-/pre-TIPS).

Results: Alpha diversity increased (Shannon and Simpson index, both $p < 0.01$) and beta diversity changed significantly (Adonis, $p = 0.002$) in HE- group while those were no significant change in HE+ group. The difference of microbiota showed that in HE-, the autochthonous taxa such as Ruminococcaceae, Lachnospiraceae and Rikenellaceae or their subordinate bacterial genus increased significantly after TIPS, moreover some harmful taxa (OHE-enriched bacteria and potential pathogenic taxa showed by previous literatures) such as Leuconostocaceae and Enterococcaceae were significantly reduced (Figure A). Meanwhile Lachnospiraceae decreased while Leuconostocaceae increased though did not withstand multiple testing correction in HE+. It was noteworthy that the synergism among harmful bacteria was significantly reduced in HE- but the HE+ group was opposite that the synergistic effect among the harmful bacteria was enhanced and the antagonistic effect between the autochthonous and harmful taxa appeared after TIPS by correlation analysis and correlation coefficient comparison (Figure B). Furthermore, multiple stepwise regression analysis was performed for the change amplitude of taxa and clinical indicators. Results showed that the decreased amplitude of Leuconostocaceae, total bilirubin and increased amplitude of Lachnospiraceae were the protective factors for development of postoperative encephalopathy and the area under receiving operating characteristics curves (AUROC) of using them was 0.784 (Figure C).

Conclusion: The occurrence of postoperative encephalopathy is closely related to the change of gut microbiota after TIPS. Specifically, the status of gut microbiota was significantly improved in HE- while the dysbiosis status in HE+ group remained poor after TIPS. Gut microbiota can be used as a potential biomarker for prevention and treatment of postoperative HE.

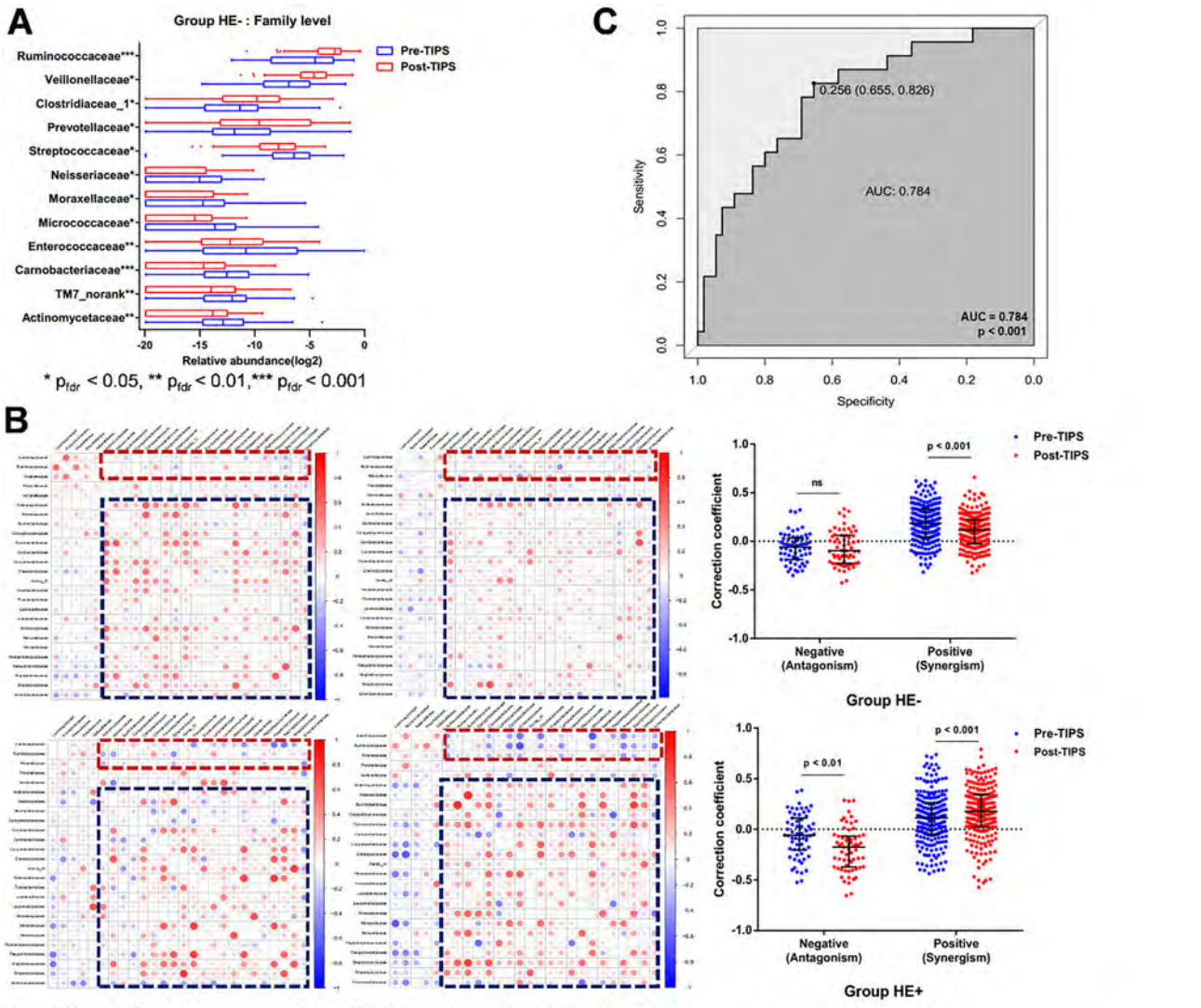

Figure: (abstract: AS111)

AS112

Roseburia spp. abundance associates with alcohol consumption in humans and its administration ameliorates alcoholic fatty liver in mice

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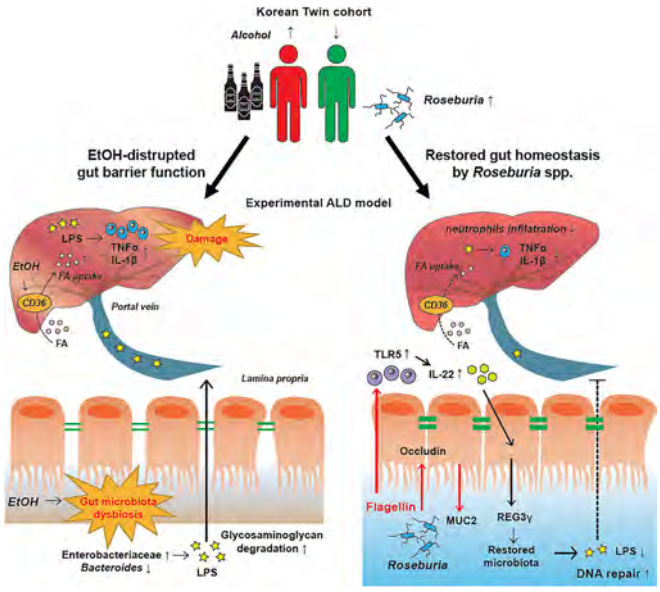
Background and Aims: Although a link between the gut microbiota and alcohol-related liver diseases (ALDs) has previously been suggested, the causative effects of specific taxa and its functions have not been fully investigated to date.

Method: Here, we analyze the gut microbiota of 410 fecal samples from 212 Korean twins using the AUDIT (Alcohol Use Disorders Identification Test) scales to adjust for host genetics. Also, the causal effects of the administration of single gut commensal strains were investigated in the experimental ALD model.

Results: This analysis revealed strong association between low AUDIT scores and abundance of the butyrate-producing genus *Roseburia*. When *Roseburia* spp. are administered to ALD murine models, both hepatic steatosis and inflammation significantly improves regardless of bacterial viability. Specifically, the flagellin of *R. intestinalis*, possibly through TLR5 recognition, recovers gut barrier integrity through upregulation of the tight junction protein Occludin and helps to restore the gut microbiota through elevated expression of *IL-22* and *REG3γ*.



Conclusion: Our study demonstrates that *Roseburia* spp. improve the gut ecosystem and prevents leaky gut, leading to ameliorated ALDs.

AS113

Gut microbiota maintains FXR activation and protects from fatal liver damage in a murine model of primary sclerosing cholangitis

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Background and Aims: Primary Sclerosing cholangitis (PSC) is a chronic cholestatic liver disease (CLD) leading to liver cirrhosis, malignant transformation and eventually hepatic failure. Gut microbiome deregulation and altered bile acid composition are prominent features of PSC. However, the functional role of gut microbiota and microbial bile acid metabolism in CLD needs to be defined. Here, we used *Mdr2*$^{-/-}$ mice as an appropriate PSC model to study the functional role of microbial bile acid metabolism for the development of CLD.

Methods: Comprehensive serum bile acid (BA) profiling was performed using UPLC-MS/MS. To characterize the functional role of microbial bile acid metabolism within the FXR-FGF15/19 axis, microbiota was modulated using broad-spectrum antibiotics (ABx). The pathophysiological consequences of this dynamic intervention was studied based on histology, flow cytometry, Matrix Assisted Laser Desorption imaging of spatial BA distribution, as well as intravital two-photon imaging of bile flux. The FXR axis was therapeutically targeted using the FXR-agonist GW4064.

Results: Microbiota depletion with ABx in adult *Mdr2*$^{-/-}$ mice prompted severe hepatic bile infarcts and devastating liver injury within 7 days. Microbiota depletion abrogated microbial bile acid metabolism, enzymatic conversion of primary conjugated bile acids into secondary bile acids resulting in the loss of FXR-mediated negative feedback suppression of Cyp7A1 and hepatic bile acid synthesis. This induced a sharp elevation of bile acid concentrations in interlobular bile ducts in a monomolecular form leading to cholangiocyte damage and bile leakage into the liver parenchyma. Therapeutic reconstitution of FXR signalling upon microbiota depletion by the FXR-agonist GW4064 completely rescued *Mdr2*$^{-/-}$ mice from this lethal phenotype.

Conclusion: This is the first report of a vital function of gut microbiota in a mammalian host. Our data define microbial bile acid metabolism as an essential compensatory modulator of CLD in a murine PSC model. This biologically intriguing and medically relevant finding opens up a new avenue for future microbiome-targeted interventions in human PSC.

AS114

Gut virome changes with disease progression in patients with cirrhosis and is inversely related to the bacterial metagenome

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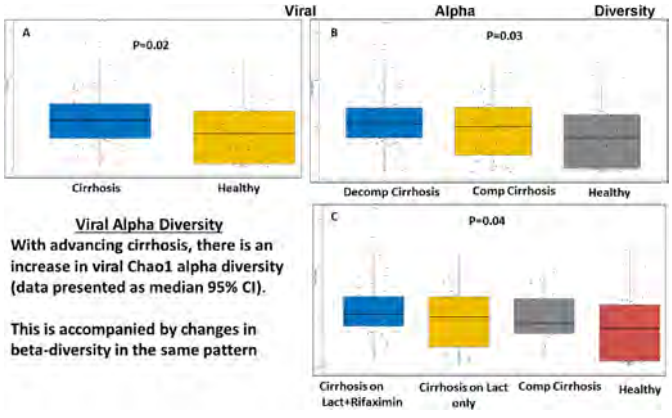
Background and Aims: Cirrhosis bacterial microbiome is linked with disease progression but the role of viromes is unclear. Aim: Define alterations in gut virome & association with bacterial microbiota as cirrhosis progresses.

Method: Healthy controls (Ctrl) & cirrhotic outpts [compensated, lactulose only (L), & on lactulose+rifaximin (L+R)] underwent stool collection for metagenomics for bacterial & viral DNA. Viral & bacterial diversity (α = within & β = between groups) & individual differentiating species were determined. Correlations between the viral and bacterial species were performed.

Results: 167 patients [40 ctrl, 42 compensated, 85 decompensated (29 on L & 56 L+R)]. MELD was lowest in compensated (median 7) vs others (L, 12, L+R, 12,p = 0.001).

Virome: α diversity: Cirrhotics had higher chao1 vs Ctrl (Fig A), decompensated ones had higher diversity than others (Fig B), & L+R had highest (Fig C). β diversity: was significant across groups(p = 0.04). MELD & viral diversity were not correlated(r = –0.1, p = 0.37). *Individual viruses*: 36 species were different, mostly Caudovirales phages & crAssphage (Cross-assembly phages; found in normal microbiota). Phages were highest against Lactobacillales, *Lactobacillus* (n = 14), *Streptococcus* (n = 1), *Enterococcus* (n = 1), then against *Enterobacteriaceae Escherichia* (n = 9), *Enterobacteria* (n = 3), *Klebseilla* (n = 2) & *Salmonella* (n = 1). Highest diversity & abundance of phages against Enterobacteriacee & Lactobacillaceae was in L+R group while crAssphages was the reverse.



Bacterial metagenome: α diversity: chao1 was lower in cirrhosis vs ctrl, decompensated vs others and lowest L+R & highest in controls (p = 7.1e −0.5). β diversity: was also different in the same pattern (p = 0.001). A weak negative correlation between MELD & chao1 was found (r = −0.22, p = 0.01). Individual species: 347 taxa, across 102 different genera were different between groups. 10 topmost ones were 3 *Lactobacillus, 2 Veillonella & 1 Enterobacteriaceae,* which were higher while *2 Lachnospira, 1 Ruminococcus, & 1 Alistipes* were lower in advanced pts.
Correlations: 10,117 significant bacterial & viral abundance correlations were found. Positive linkages were between phages & bacterial targets (Enterobacteria, Escherichia, Lactobacillus). Negatively linked were Lactobacillus phages & beneficial taxa (Lachnospiraceae, Clostridiaceae & Ruminococcaceae). crAssphages were negatively linked with Enterobacteriaceae.
Conclusion: With decompensation, virome diversity increases but abundance decreases, which is opposite of bacteria that reduce in diversity with decompensation. Cirrhosis gut virome consists of phages targeted towards Lactobacillus & Escherichia, which increase & crAssphages which decrease with decompensation. Knowledge of phages could enhance drug discovery against bacteria that are linked with cirrhosis progression.

Liver immunology

AS115
Interferon-gamma and CTLA-4 drive liver-induced systemic CD4 T cell tolerance

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Background and Aims: We have previously shown that ectopic expression of myelin basic protein (MBP) in the liver can prevent autoimmune encephalomyelitis (EAE); however, the mechanisms explaining how the liver can effectively protect distant tissues are not entirely clear.
Method: MBP-specific tg4 T cells were adoptively transferred into CRP-MBP mice expressing MBP in the liver. These congenic T cells were re-analysed *ex vivo* following antigen-recognition in the liver to identify tolerance-associated molecules. Blocking antibodies were used to test the importance of the identified molecules for the protection from autoimmune neuroinflammation in CRP-MBP mice.
Results: Transferred tg4 T cells upregulated IFN-gamma and accumulated in the livers of CRP-MBP recipients, as compared to non-transgenic littermates (> 10-fold). T cell accumulation was dependent on IFN-gamma-induced activation of the CXCL9 - CXCR3 axis, which enabled endothelial transmigration. Interestingly, IL-10 production was induced in transferred tg4 T cells in CRP-MBP mice and some of these T cells displayed a CD49+ Lag-3+ Tr1-like phenotype. However, inhibition of IL-10 via *in vivo* antibody blockade did not break tolerance. In addition to Lag-3, the accumulated tg4 T cells in the livers of CRP-MBP mice significantly upregulated several co-inhibitory receptors together with IFN-gamma, including PD-1, Tim-3, TIGIT and, most notably, CTLA-4. However, blockade of CTLA-4 alone by *in vivo* administration of an anti-CTLA-4 antibody did not impair tolerance. In contrast, blockade of IFN-gamma reduced expression of *Cxcr3* and *Cxcl9* and prevented hepatic accumulation of tg4 T cells, resulting in partial impairment of systemic tolerance and development of mild EAE. Intriguingly, concomitant blockade of IFN-gamma and CTLA-4 completely abolished tolerance to MBP and induced severe EAE.
Conclusion: Our findings demonstrate that systemic CD4 T cell tolerance induction in the liver and resulting protection from autoimmune disease depends on 1) IFN-gamma/CXCL9/CXCR3-mediated accumulation of autoreactive T cells in the liver and 2) up-regulation of multiple co-inhibitory receptors, notably CTLA-4.

AS116
TIMD4 expression distinguishes a population of self-renewing human liver macrophages

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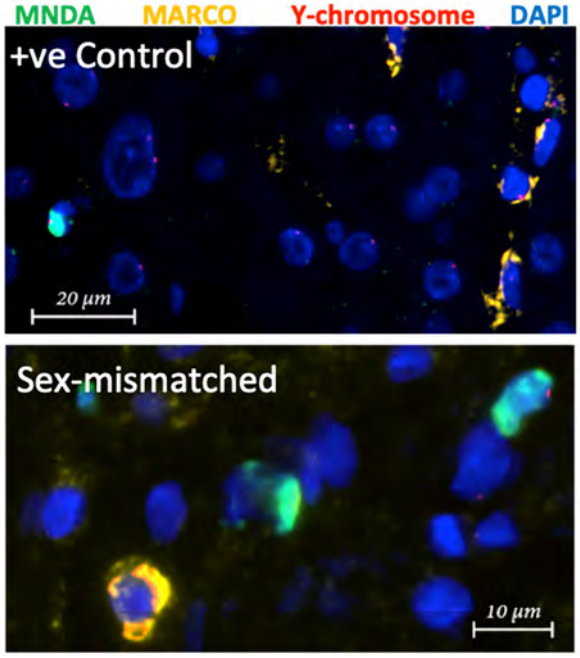
Background and Aims: Hepatic macrophages play a key role in liver health and disease. Recent work in mice shows that liver macrophages can be divided into two ontogenically-distinct subsets – tissue-resident Kupffer Cells (KC) which are embryologically-derived and self-renew throughout adult life and monocyte-derived macrophages (MDM) which derive from recruited blood monocytes. Murine KC and MDM populations have distinct functions in regulating liver homeostasis and injury. However, there remains minimal definition of the ontogeny of human liver macrophages. We aimed to determine whether human KCs are long-lived and self-renewing.
Method: We interrogated single-cell RNA-sequencing (scRNAseq) data from human liver samples generated via the 10X Genomics platform and analyzed using the Seurat R-package. Y-chromosome fluorescent in-situ hybridization probe (Y-FISH) staining was performed on archival liver biopsy sections from patients who underwent sex-mismatched liver transplantation. Experimental samples were male recipient-female donor patients, whilst male recipient-male donor and female recipient-female donor served as positive and negative controls respectively. Y-FISH staining was combined with multiplex fluorescent immunofluorescence (IHCF) to enable simultaneous detection of macrophage subpopulation markers. Images were analyzed using Fiji software.



Results: Analysis of scRNAseq data distinguished 3 populations of human liver macrophage; MNDA+MARCO-TIMD4-, MNDA-MARCO +TIMD4+ and MNDA-MARCO-TIMD4+. IHCF staining demonstrated

that MNDA+ macrophages had a monocyte-like morphology. Combined IHCF and Y-FISH staining on female-to-male transplant biopsies confirmed all MNDA+ cells to be Y-chromosome positive, highlighting MNDA as a marker of human liver MDMs. In contrast, MARCO+ macrophages were only 27.84% Y-FISH positive (Figure). This low level Y-FISH positivity remained consistent for up to 5 years post-transplant. Combined TIMD4 and Y-FISH staining indicated lower Y-chromosome positivity than MARCO+ macrophages, defining TIMD4 as the more distinguishing marker of long-lived self-renewing human KCs.

Conclusion: This study demonstrates ontological heterogeneity within the human liver macrophage compartment for the first time. The markers MNDA and TIMD4 allow distinction of circulation-derived and liver resident macrophages and in the future can be used to enable functional analyses of ontogenically-distinct macrophage subpopulations in health and disease.

AS117

Targeting p53 and histone methyltransferases to restore fully exhausted CD8+ T cells in human HCV infection before and after DAA-therapy

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Background and Aims: New direct-acting anti-virals (DAA) can cure the great majority of chronic HCV infections but a limited proportion of patients who do not respond to therapy, especially those who fail more than one retreatment, might benefit from immune modulation. In order to deepen our understanding of CD8 T cell exhaustion as a general mechanism of virus escape and identify suitable molecular targets to restore an efficient anti-viral CD8 T cell function as a candidate immune reconstitution therapy for chronic HCV infection, aim of our study was to characterize deregulated genes and pathways underlying early and late HCV-specific CD8 T cell exhaustion.

Method: Genome-wide expression profiling was performed on HCV-specific CD8 T cells in early and late acute HCV infection and in chronic HCV patients. Deregulated pathways were validated by flow-cytometry and studied also in DAA-treated chronic patients. Target-specific compounds were tested for their ability to correct dysregulated cell functions and reconstitute antiviral activity in acute and chronic HCV infection.

Results: Early development of CD8+ T cell exhaustion was marked by the up-regulation of genes related to oxidative phosphorylation and TCA cycle and the down-regulation of glycolysis-related transcripts, in the context of a predominant transcriptional up-regulation. This condition evolved in chronic HCV patients into a broader metabolic down-regulation associated to deregulated chromatin histone marks and epigenetic control. A strong improvement of HCV-specific CD8 T cell metabolic and antiviral functions was induced by pharmacological inhibition of p53 and of G9a and EZH2 histone methyltransferase activity. In chronic DAA-treated patients, a complete correction of metabolic and repressive histone methylation marks was not obtained in virus-specific CD8+ T cells.

Conclusion: Fully exhausted CD8+ cells are characterized by a widespread transcriptional down-regulation that may primarily result from epigenetic silencing. A number of metabolic and functional T cell defects appear to be present in exhausted HCV-specific CD8+ cells from chronic HCV patients with lack of full restoration after DAA-therapy. HMTs/p53 inhibitors may represent possible candidates for combination therapies with DAA in HCV-positive patients not properly responding to last-generation anti-virals and as novel and effective T cell reconstitution strategies for other T cell exhaustion-associated diseases.

AS118

Controlling regulatory T cell populations in the liver by enclysis, a CD4+ T cell engulfment process

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Background and Aims: Regulatory T cells (Treg) dampen inflammation and they are increased in the liver compared to blood, contributing to a tolerising environment. The swift neutralisation of Treg cells is important to enable immune effector functions to combat infection, but the mode of this is not understood. We noted that hepatocytes preferentially engulfed live Treg cells, and we set out to characterise the mechanism and outcome of this new phenomenon we termed "enclysis."

Method: We measured enclysis, the enclosure and lysis of Treg cells, *in vitro* and *ex vivo* using perfused liver wedges, in the presence of inhibitors of known cell-in-cell processes. Reporter dyes for viability, mitochondrial activity and acidification were used to determine enclysis outcome. Cell-in-cell structures were documented by light, confocal, electron and multiphoton microscopy. Foxp3+ Treg and T-bet+ T helper cells were enumerated in donor and in end-stage disease livers of AIH, PBC, PSC, ALD, NASH, HBV and HCV origin.

Results: Hepatocytes preferentially engulfed live Treg cells in a process that differed in mechanism and kinetic to previously described cell-in-cell structures (efferocytosis, suicidal emperipolesis, entosis). Enclysis reflected the enclosure and lysis of Treg cells inside hepatocytes, and enclytic vesicles were connected to the endocytic pathway. Enclysis was increased in patients with autoimmune compared to viral hepatitis ($p = 0.0011$).

Conclusion: Enclysis is the preferential engulfment and deletion of live Treg cells by hepatocytes and can be modulated pharmacologically, offering a new therapeutic target for immune regulation in the liver.

AS119

T cell receptor-engineered mucosal-associated invariant T cells with antiviral cytotoxic potential against hepatitis virus replicating hepatoma cells

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Background and Aims: Virus-specific T cells are known to be protective against hepatitis B (HBV) and hepatitis C (HCV) infections.

Mucosal-associated invariant T (MAIT) cells are a $CD3^+TCRValpha7.2^+CD161^+$ T cell subset which is naturally enriched in the liver. Because of their inherent liver-homing capacity they may represent a novel therapeutic alternative for hepatitis virus-associated liver diseases, including liver cancer, if they express the virus-specific T cell receptors (TCRs). The aim of this study was to compare the function of TCR-redirected MAIT cells with conventional T (ConT) cells that are currently being used in cancer immunotherapy.

Method: Donor-matched MAIT cells and ConT cells from healthy donor peripheral blood were redirected with HBV-Env183-TCR or HCV-NS31073-TCR mRNA. Surface expression of virus-specific TCR was quantified by flow cytometry. Real-time killing assays (xCELLigence) were performed with the HBV-expressing hepatoma cell line HepG2.2.15, with HBV peptide pulsed/unpulsed HepG2 cells as controls. T cell responses against HCV was assessed in Huh-7/Lunet HCV replicon cells using a luciferase read-out system. Intracellular cytokine staining following target cell coculture was also done in parallel to assess the polyfunctional profiles.

Results: Expression of HBV and HCV TCR transgenes in MAIT cells was comparable to ConT cells after TCR-redirection. HBV TCR-MAIT cells displayed an antigen-specific, rapid and potent cytolytic capacity, similar to that of ConT cells, resulting in total killing of HepG2.2.15 cells by experimental end-point. Similarly, HCV TCR-MAIT cells reduced HCV replicon luciferase expression in an HLA- and dose-dependent manner. Following coculture with hepatoma target cells, virus-specific MAIT cells were not only capable of degranulating and producing IFNγ and TNF, they also secreted the pro-inflammatory cytokine IL17, an effect not observed in conventional T cells.

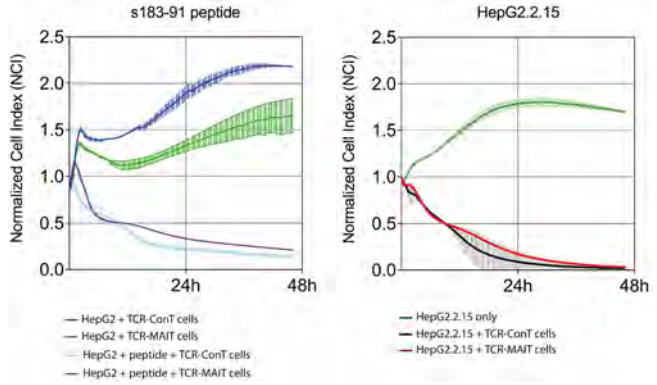

Figure: Real-time cytotoxicity assay of TCR-redirected ConT and MAIT cells with HepG2 cells (negative control), HepG2 cells pulsed with HBV envelope s183-91 peptide (positive control), and the full-HBV expressing cell line, HepG2.2.15.

Conclusion: TCR-redirected MAIT cells display comparable cytotoxic potential to conventional T cells. Further studies are required to compare the target-specific effects in the liver microenvironment.

AS120

Metabolic programming of exhausted CD8 T cells in chronic viral hepatitis

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Background and Aims: Accumulation of exhausted T cells (T_{EX}) is a major concern in patients with chronic hepatitis B and C virus (HBV/HCV) infection. These T_{EX} are characterized by an increased inhibitory receptor expression, poor effector function and substantial changes in their transcriptional profile compared to functional T cells. The regulation of energy metabolism is thought to induce dysfunction of T_{EX}. However, the metabolic programs of HBV- and HCV-specific CD8T cells in chronic infection and their links to T cell function remain poorly characterized.

Method: We profiled key metabolic pathways involved in energy metabolism in patients with cHBV and cHCV using metabolism-directed flow cytometry and transcriptome analysis.

Results: In chronic infection, HCV-specific CD8T cells exhibit enhanced glucose uptake but reduced mitochondrial polarization when compared to HBV-specific CD8T cells. These features were linked to the higher expression of inhibitory receptors suggesting more severe exhaustion in HCV infection. Therapy with direct antiviral agents induced an accumulation of HCV-specific CD8T cells after two weeks, but did not fully reprogram the metabolic phenotype of these cells. Interestingly, glucose uptake remained stable, but the uptake of long-chain fatty acids increased and depolarized mitochondria decreased upon therapy. Transcriptome analysis of metabolic pathways revealed an upregulation of *ACSS1/ACSS2* mRNA encoding for acetyl-CoA synthetase in HCV-specific CD8T cells, suggesting a higher ability to metabolize acetate as a potential anaplerotic TCA substrate. Addition of acetate to exhausted CD8T cells obtained from cHCV patients was able to improve functional exhaustion.

Conclusion: These results demonstrate differential metabolic regulation of HBV- and HCV-specific CD8 T cells. The elucidation of the molecular mechanisms underlying these distinct metabolic programs will allow metabolism-directed interventions to improve T cell function.

FRI356

Interleukin-15 restores the reactivity of the peripheral memory-like pool in the exhausted hepatitis B virus-specific CD8+ T cell population during persistent HBeAg(-) infection

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Background and Aims: The peripheral CD8T cell memory-like (MLP) subset is responsible for tissue surveillance and maintaining an exhausted effector response during chronic viral infections. This population is characterised by TCF1 expression and increased size and complexity after Ag encounter. In persistent infections such as hepatitis B virus (HBV) eAg(-) chronic hepatitis (CHB), IL-15 could induce the homeostatic proliferation of this pool after a metabolic reset, leading to the generation of a progeny (P) with improved effector abilities.

Method: In 6 HLA-A2+ eAg(-) CHB patients coinfected with cytomegalovirus CMV, longitudinal tracking of Ag-specific CD8T cells was carried out. Lymphocytes were in-vitro challenged for 20 days with HBVcore18–27 or CMVpp65495-504 peptides in presence of IL-2 or IL-15. Ag-specific CD8T cells were visualized by staining with labelled HLA-A2/peptide pentameric complexes (pentamer) by flow cytometry. MLP pool was gated on Pentamer+ TCF1+ FSChigh population and the P subset on the Pentamer+ TCF1- gate. On day 7, PD-1, CD127, Glut1, Mitotracker green (MTG), PGC1α phenotype in the MLP pool and on day 12, the effector function (IFNγ, TNFα, CD107a) in the P subset were tested.

Results: The kinetics of HBV-specific CD8 MLP pool with IL-2 treatment was different between CMV and HBV. Specifically, the number of MLP cells in HBV was 10-folds lower in the peak day of this pool's proliferation and this gave rise to a P subset that was 12-folds lower than for CMV-specific cells on day 12 ($p < 0.05$), (Fig 1). HBV-specific MLP population showed higher PD-1, Glut1 and lower CD127, MTG, PGC1α expression than CMV-specific progenitors ($p < 0.05$).

This correlated with lower IFNγ, TNFα secretion, and lower CD107a expression on HBV-specific P than on the CMV-specific subset ($p < 0.05$). IL-15 in-vitro treatment of HBV-specific CD8 cells increased 6-folds the MLP pool on day 7 and maintained this population up to day 9 with a later progressive decrease (Fig 1). This change on the MLP kinetics correlated with a decrease of Glut1 level and an increase in PGC1α expression ($p < 0.05$) linked to an improvement of the P pool effector abilities on day 12 ($p < 0.05$).

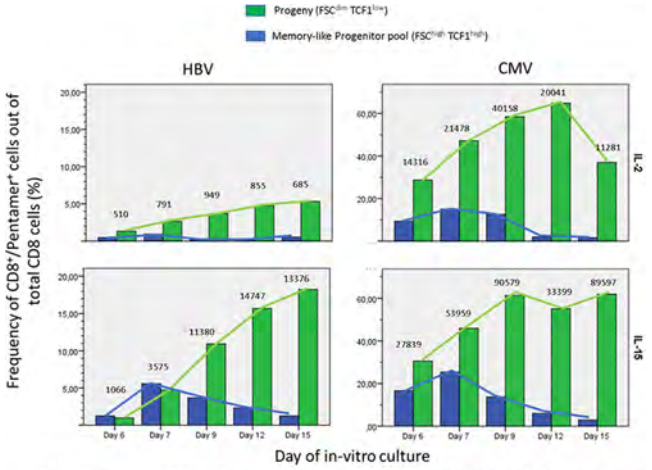

Fig 1. HBV-core$_{18-27}$ and CMV pp65$_{495-504}$ memory like progenitor and progeny pool kinetics in a representative CHB eAg negative CMV co-infected patient during Ag-specific in-vitro challenge. Figures on top of bars represent the absolute number of CD8+/Pentamer+ cells isolated per culture well in each experimental condition.

Conclusion: IL-15 in-vitro treatment increases the memory-like pool and modifies its metabolism to a less glycolytic one that leads to an improvement in the effector abilities of the progeny.

Immune-mediated and chronic cholestasic liver disease – Clinical aspects

AS121

The impact of geographical region on outcomes of patients with primary biliary cholangitis from western Europe

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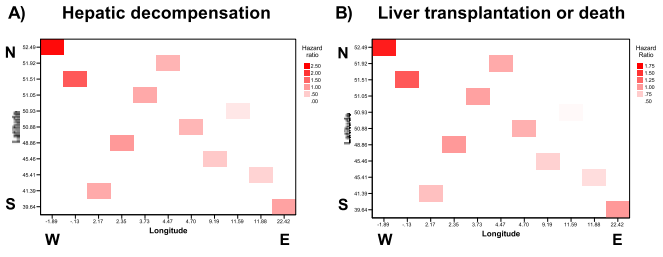
Background and Aims: Although the incidence and prevalence rates of primary biliary cholangitis (PBC) vary according to geographical region, the disease affects people from all geographical regions. It is unknown whether regions with a higher prevalence for PBC, such as Northern Europe, have distinct disease characteristics or outcomes. The aim of this study was to determine whether geographical region contributes to differences in outcomes of patients with PBC within Western Europe.

Method: Patients from the Global PBC database from European centers diagnosed from 1990 onwards that were ursodeoxycholic-acid (UDCA) treated were included in the study. Patients with a time lag greater than 1 year from diagnosis to the start of follow-up were excluded. Differences in baseline characteristics and outcomes (transplant-free survival and decompensation) were studied. The impact of geographical region was studied according to North/South and East/West, as well and longitude and latitude.

Results: A total of 1878 patients were included in the study. Patients in North Europe were more often of a moderately advanced or advanced Rotterdam biochemical stage (28.4%) compared to those in South Europe (20.6%). Additionally, they exhibited higher median alkaline phosphatase (ALP [2.0 × ULN vs. 1.4 × ULN]) and transaminases (AST: 1.4 × ULN vs. 1.3 × ULN; ALT: 1.7 × ULN vs. 1.4 × ULN). Similarly, West Europe also presented with higher ALP and transaminases. North Europe, as compared to South Europe, was associated with lower transplant-free survival and higher decompensation rates, with 15-year survival rates of 66% vs 79% ($P = 0.001$) and decompensation incidence of 21% vs 10% ($P < 0.001$). The association of geographical region with outcome was assessed with longitude and latitude in multivariable analysis while adjusting for biochemical markers of disease severity and cirrhosis as a time-dependent covariate, as well as age, sex, and diagnosis year. There was a significant interaction between latitude and longitude in the prediction of transplant-free survival ($P = 0.001$) and decompensation ($P < 0.001$). An increased risk for poor outcomes was observed for the Northwestern area of the evaluated region compared to the reference (Paris) (Figure).



Conclusion: Patients from Northwestern Europe with PBC and of similar disease severity have increased risk of decompensation and liver transplantation of death. This suggests that in the Northwestern part of Europe, geographical region may have an impact on patient outcome.

AS122

Combination of quantitative 3D MRCP and multi-parametric MRI demonstrates increased periductal iron-corrected T1 in large-duct primary sclerosing cholangitis

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Background and Aims: One of the features of primary sclerosing cholangitis (PSC) is a characteristic "onion skin" periductal fibrosis usually seen on liver biopsy. The aim of this study was to evaluate whether a related feature to this can be diagnosed macroscopically from quantitative MRI scans.
Method: Standardised 3D MRCP and axial liver T1 and T2* maps were acquired on patients with a known diagnosis of large-duct PSC and healthy participants. LiverMultiScan (Perspectum Diagnostics (PD), Oxford, UK) was used to generate axial maps with cT1 measurements at each voxel over multiple slices in the liver. Biliary data was analysed using MRCP+ (PD, Oxford, UK) to build a parametric biliary tree model which was aligned to the axial liver cT1 maps as demonstrated in Figure 1. Periductal cT1 was quantified over fixed radial distances surrounding the bile ducts at 1 mm increments up to 10 mm, restricted to a delineation of the liver that excluded prominent blood vessels. Region of interest (ROI) 1 was defined as the ring-shaped area between the circles with radius 2 and 5 mm. ROI 2 was the area between circles with radius 6 and 9 mm. Mean cT1 was measured in each ROI and compared to the mean cT1 for the whole axial segment (reference), using the Friedman test with Dunn's post-hoc correction for multiple comparisons. Advanced fibrosis (≥ F3) was defined according to transient elastography (Echosens, France) liver stiffness measurement (LSM) cut-off of 9.6 kPa.

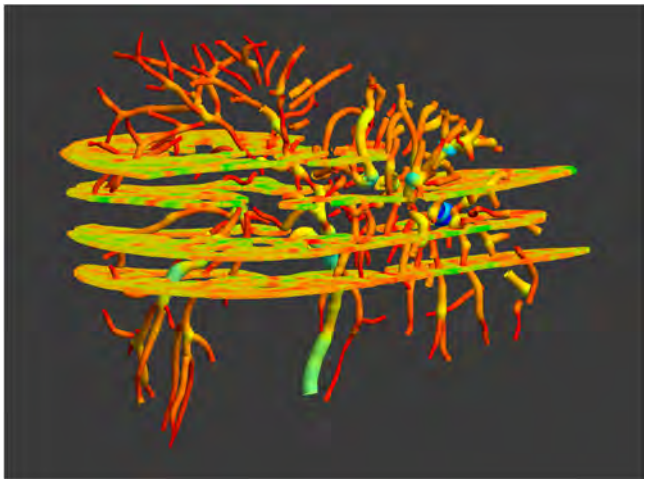

Figure 1: Co-registration of the biliary tree model to four axial liver cT1 maps in a patient with PSC for quantification of periductal cT1.

Results: Fifty eight patients (67% male) with median age of 47 years (range: 18–76) and median PSC duration of 8 years (range: 1–25) as well as ten healthy participants (70% male) with median age 33 years (range: 25–44) were recruited. There was a significant difference in mean cT1 over the three regions ($p < 0.0001$) in PSC but no difference was observed in healthy participants. Pairwise comparisons in PSC showed mean cT1 in ROI 1 (780 ms) was higher than ROI 2 (764 ms; $p < 0.0001$) and reference (765 ms; $p < 0.0001$) but there was no difference between ROI 2 and reference ($p = 0.15$). Importantly, the mean cT1 in ROI 1 was higher in PSC with advanced fibrosis on LSM (815 vs 770 ms, $p = 0.02$). A cut-off of 774 ms had an area under the receiver operating characteristics curve (AUROC) of 0.72 (95% CI 0.54–0.89, $p = 0.01$) to identify advanced fibrosis.
Conclusion: Periductal cT1 in the ring of tissue 2–5 mm around the bile ducts is significantly higher than regions further from the bile ducts in PSC and may represent a macroscopic finding that correlates to the histologic "onion skin" fibrosis. This demonstrates how quantitative MRI techniques can be used to assess features of disease that were previously seen only at histology. Follow-up data from this study will assess the ability of periductal cT1 to predict fibrosis progression and clinical endpoints.

AS123

Heterozygous carriers of ABCB4 mutations show a mild clinical course, but impaired quality of life and limited risk for cholangiocarcinoma – a cohort study

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Background and Aims: Carriers of ATP binding cassette B4 (ABCB4) mutations may develop progressive familial intrahepatic cholestasis type 3 (PFIC3) with biliary cirrhosis, low-phospholipid-associated cholelithiasis (LPAC), intrahepatic cholestasis of pregnancy (ICP) and/or persistent hepatocellular secretory failure (PHSF) or may remain free of clinical complications. Here, the clinical long-term course, quality of life and histological re-evaluation according to Nakanuma were investigated in a cohort of heterozygous carriers of ABCB4 mutations.
Method: In this bicenter cohort study, adult individuals with a proven ABCB4 mutation were analyzed. Participants underwent history taking, physical examination, blood analysis, abdominal ultrasound (US) and elastography (Fibroscan®) and were asked to complete a 36 Item Short Form Health Survey (SF36) regarding quality of life and Visual Analogue Scale (VAS) for pruritus. Past clinical findings were collected from electronic patient files. All available liver biopsies were re-classified according to the Nakanuma staging system. Outcome of quality-of-life-data was compared to that published for patients with primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and the general population.
Results: Sixty-seven patients were identified of whom 64 (96%) were alive at inclusion into the study and 63 (94%) were treated with ursodeoxycholic acid. Two patients died of cholangiocarcinoma and one of decompensated biliary cirrhosis. Three more deaths of cholangiocarcinoma were reported in first degree relatives of participants without available genetic analysis. Overall transplant-free survival was 91% (average time from first presentation 16 years). Liver stiffness was normal (<6.3 kPa) in 75%, and microcalcifications were detected at ultrasound in 22% of cases. Quality of life (SF-36, n = 48) was lower than that of the general population especially in the energy/fatigue and general health domains and comparable to that reported for PSC patients. The Nakanuma scoring system applied in 15 available histological specimens reflected the clinical disease course.
Conclusion: Heterozygous carriers of an ABCB4 mutation have a mild clinical course, but impaired quality of life and limited risk of cholangiocarcinoma. Use of Nakanuma staging appears feasible for histological evaluation in ABCB4 deficiency.

AS124

The effect of chyme reinfusion on the bile salt/fibroblast growth factor 19 signaling axis in intestinal failure patients with a temporary jejunal double enterostomy

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Background and Aims: Temporary jejunal double enterostomies may result in intestinal failure (IF) and require parenteral nutrition (PN). Etiology of IF-associated liver disease (IFALD) is multifactorial, and involves PN and enterohepatic circulation (EHC) disruption. Chyme reinfusion (CR) improves IF and liver abnormalities and restores EHC. Bile salts are signaling molecules undergoing EHC and negatively regulate their own synthesis via endocrine FGF19 produced in the ileum. Here we tested the hypothesis that functional restoration of the EHC and attendant bile salt/FGF19 signaling contributes to the beneficial effects of CR.

Method: IF patients with a double jejunal enterostomy on PN were recruited for CR treatment in a tertiary referral center (RESCUE study: ClinicalTrial.gov NCT02990195). Blood samples were collected prior to, at start, and 1, 3, 5 and 7 weeks after CR initiation. Ileum biopsies were taken prior to and 3 weeks after start of CR. Plasma levels of FGF19, total bile salts (TBS), 7alpha-hydroxy-4-cholesten-3-one (C4, a plasma marker of bile salts synthesis), citrulline, bile salt composition, and serum liver injury and cholestasis markers were determined. A linear mixed model was used to evaluate the (temporal) relationship between citrulline, TBS and FGF19 and biochemical/clinical outcomes.

Results: Twelve patients (5 females, age 67.7 ± 14.6 y) were included. Elevated serum markers for cholestasis (GGT, ALP) (both $p < 0.01$) and liver injury (ALT, AST) normalized after CR, and hypoalbuminemia was corrected reflecting improved nutritional status ($p < 0.001$). CR resulted in improved intestinal function, as inferred from elevated plasma citrulline from week 1 onwards and enhanced mRNA expression of epithelium-specific genes (e.g. *FXR*, *OSTa/b*). Plasma FGF19 was increased after CR and peaked after 1 week (0.034 ± 0.030 ng/mL at baseline vs 0.141 ± 0.080 ng/mL at 1 week, $p < 0.01$). This was accompanied by normalization of plasma C4 which was elevated at baseline, and reduced circulating TBS levels (both $p < 0.05$). CR altered the composition of the circulating bile salts pool: the increased fractions of gut-microbiota derived unconjugated and secondary bile salts (both $p < 0.05$) reflected restored contact between bile and the gut microbiota.

Conclusion: CR treatment improves liver and intestinal function in IF patients with a jejunal enterostomy. The beneficial effect of CR is partly mediated by bile salt/FGF19 signaling, resulting in restored homeostatic regulation of bile salt synthesis.

AS125

Patients with autoimmune hepatitis and liver cirrhosis have disease activity despite normal transaminases

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Background and Aims: In autoimmune hepatitis (AIH) serum aminotransferase and immunoglobulin G (IgG) levels within the normal ranges define biochemical remission and are considered as surrogate markers for histological remission. However, it remains unclear to what extent these parameters predict histological activity in patients with AIH and liver cirrhosis.

Method: In a European multicentre retrospective study we included 125 biopsies from 113 patients with AIH and histologically proven liver cirrhosis and with available biochemistry parameters at time of biopsy. (Hamburg: n = 69, Larissa: n = 26, Hannover: n = 19, Nijmegen: n = 10, London: n = 1). As control group we identified 71 biopsies of 69 patients from Medical University Centre Hamburg-Eppendorf with diagnosis of AIH but without liver cirrhosis. Data were assessed at time of biopsy and at last follow-up.

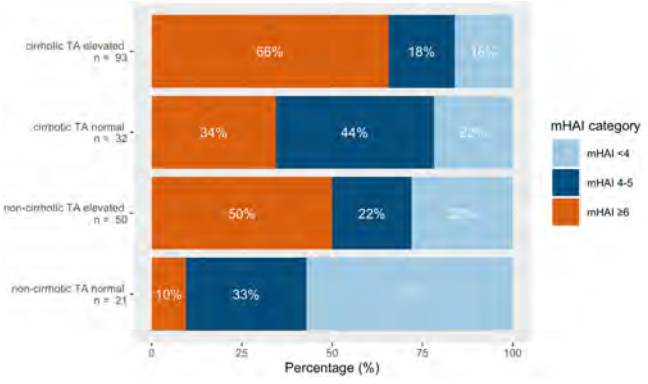

Figure 1: Histological activity scores subdivided as histological remission (mHAI <4), mild residual disease activity (mHAI 4–5) or moderate to high inflammatory activity (mHAI ≥ 6) in AIH patients with and without liver cirrhosis and serum aminotransferase levels within the normal range. TA, aminotransferases; mHAI, modified hepatitis activity index.

Results: In patients with AIH liver cirrhosis and elevated transaminases (n = 93) 66% presented with moderate to high histological activity (mHAI ≥ 6) (Fig. 1). Normal aminotransferases were seen in 26% (32/125) of patients with AIH and liver cirrhosis. Of these, only 22% (7/32) had histological remission (mHAI <4), 44% (14/32) presented with residual (mHAI 4–5) and 34% (11/32) with moderate to high inflammatory activity (mHAI ≥ 6). In contrast, in 43% (9/21) ($p = 0.019$) of AIH patients without cirrhosis and normal aminotransferase levels possessed histological activity of ≥ 4/18 points. The addition of IgG to define complete biochemical remission

(transaminases and IgG within normal ranges) improved the prediction of moderate to high histological activity in only 2/12 patients with AIH liver cirrhosis presenting with mHAI ≥ 6. However, 67% of patients with AIH and cirrhosis and complete biochemical remission had mHAI ≥ 4.
Conclusion: Patients with AIH cirrhosis and transaminases within the normal range may still have AIH activity that warrants intensified immunosuppressive therapy. The addition of serum IgG levels may improve the diagnostic performance of biochemistry. Our results indicate that biochemical parameters alone do not accurately predict AIH disease activity in cirrhosis.

AS126
Autoimmune hepatitis and cancer risk – a Danish nationwide cohort study

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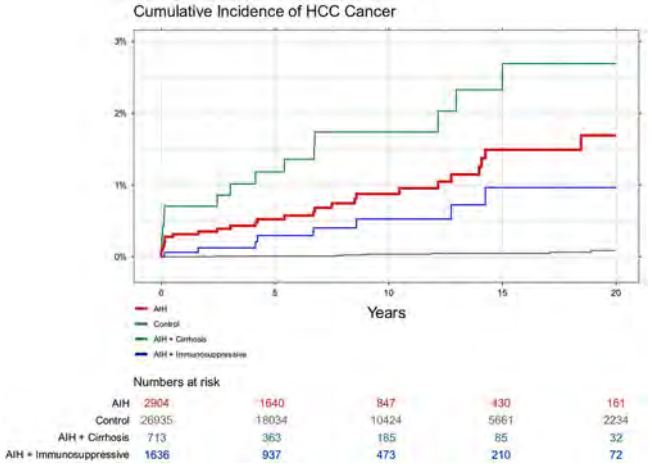
Background and Aims: Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease, and the chronic inflammation may cause cancer development. We examined cancer risk in a nationwide cohort of patients with AIH.
Method: We identified all Danish citizens diagnosed with AIH between 1994 and 2018 and followed them through Danish healthcare registries. For each of the 2,904 patients with AIH we included 10 population controls matched on gender, age, and year of birth. We examined absolute and relative risks of hepatocellular carcinoma (HCC) and other cancers (non-HCC-cancers) using the cumulative incidence function and Cox proportional hazards regression. Within the cohort of AIH patients, we assessed relative risks of HCC and non-HCC-cancers for patients with vs. without cirrhosis and on vs. off immunosuppressive treatment.
Results: The 20-year risk of HCC was 1.7% [95% confidence interval (CI): 1.1–2.6] for patients with AIH vs. 0.1% [95% CI: 0.0–0.2] for controls. For AIH patients with and without cirrhosis the 20-year risk of HCC was 2.7% [95% CI: 1.5–4.5] and 1.3% [95% CI: 0.6–2.4], respectively, while the risk was 1.0% [95% CI: 0.4–2.0] and 2.4% [95% CI: 1.4–3.9] for patients on vs. off immunosuppressive treatment (Figure). Among patients with AIH, cirrhosis was associated with HCC (hazard ratio = 7.6 [95% CI: 3.3–17.8]), but not with non-HCC-cancers (hazard ratio = 1.2 [95% CI: 1.0–1.5]). Immunosuppressive treatment exerted a protective effect against HCC development (hazard ratio = 0.3 [95% CI: 0.1–0.7]), but was associated to non-HCC-cancers (hazard ratio = 1.3 [95% CI: 1.0–1.6]).



Conclusion: AIH was associated with an increased 20-year risk of HCC in comparison with controls, but the absolute risk excess was small: 1.6% over a 20-year period. Among patients with AIH, cirrhosis was associated with an increased risk of HCC while immunosuppressive treatment, by contrast, reduced the risk.

Molecular and cellular biology

AS127
The role of ferroptosis in chronic liver disease

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Background and Aims: The prevalence of non-alcoholic fatty liver disease, ranging from steatosis to non-alcoholic steatohepatitis (NASH), is increasing in developed countries. In some patients, progression towards cirrhosis and hepatocellular carcinoma (HCC) occurs. To present, the underlying mechanisms for disease progression remain incompletely understood. In NASH oxidative stress and lipid peroxidation constitute prominent features and may hence play a key role. Interestingly, accumulation of lipid peroxides can trigger ferroptosis, an iron-dependent mode of cell death. According to *in vitro* studies, acyl-CoA synthetase long-chain family member 4 (ACSL4) is an essential contributor to ferroptosis. In our study, we aimed to investigate the relevance of ferroptosis for disease progression using hepatocyte-specific ACSL4 inhibition in experimental models of chronic liver disease.
Method: Primary hepatocytes from either wild-type (WT) mice or mice with hepatocyte-specific deletion of ACSL4 ($ACSL4^{\Delta hepa}$) were treated with specific inducers (e.g., RSL3) and inhibitors (e.g., Liproxstatin-1) of ferroptosis. In addition, we compared disease development between WT and $ACSL4^{\Delta hepa}$ mice to investigate the role of ferroptosis. We used a high-fat diet (HFD) to trigger NASH and STZ (Streptozocin) with HFD as a NASH-HCC model.
Results: Treatment of primary hepatocytes with RSL3 leads to increased cell death, which could be rescued by adding Liproxstatin-1 or by using ACSL4-deficient hepatocytes.
In our HFD-based NASH model, we did not find significant differences between WT and $ACSL4^{\Delta hepa}$ mice. Specifically, liver-to-body weight ratio, serum transaminase levels, and immune cell infiltration were not altered. In contrast, in our NASH-HCC model, inhibition of ferroptosis in hepatocytes augments chronic liver disease resulting in increased serum transaminase levels in $ACSL4^{\Delta hepa}$ mice. Importantly, while the overall tumor burden was not affected in $ACSL4^{\Delta hepa}$ mice, the number of smaller tumors was significantly increased.
Conclusion: Our results demonstrate that primary mouse hepatocytes are susceptible to induction of ferroptosis and that this mode of cell death depends on functional ACSL4. Interestingly, ferroptosis seems to be a protective mechanism during tumor initiation, by regulating lipid accumulation and cell death in hepatocytes. Therefore, activation of ferroptosis or inhibiting key molecules regulating cell death, can be a possible therapeutic treatment for human disease.

AS128

The NADPH oxidase NOX4 regulates lipid metabolism, which contributes to its tumour suppressor actions in hepatocellular carcinoma

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Background and Aims: The NADPH oxidase (NOX) family has emerged in the last years as an important source of reactive oxygen species (ROS) in signal transduction. The isoform NOX4 has been implicated in a variety of physiological and pathological processes. In recent works, we found that stable knockdown of NOX4 expression in liver tumor cells increases their proliferative capacity in vitro and enhances their tumorigenic potential in xenografts in mice, resulting in earlier onset of tumor formation and increase in tumor size (Crosas-Molist et al., Free Radic Biol Med 2014). NOX4 could also regulate other cellular processes that occur later in progression and that favor tumor metastasis, such as migration and invasion (Crosas-Molist et al., Oncogene 2016). NOX4 gene deletions are frequent in HCC patients, correlating with higher tumour grade. Here we aim to determine the cellular and molecular mechanisms regulated by NOX4 in liver cells that could explain its tumor suppressor functions.
Method: Cell models: HCC cells (PLC/PRF/5 and SNU449) were NOX4 was either silenced (ShRNA) or overexpressed. Transcriptomics, Proteomic and Metabolomic analyses. Metabolomic profile through Seahorse technology. Analysis of mitochondria structure and function. Analysis at real time of cell adhesion, proliferation and migration through xCELLigence technology.
Results: A proteomic analysis, by comparing control cells with HCC cells where NOX4 had been silenced or overexpressed, allowed the identification of metabolism as one of the highest affected processes. Silencing NOX4 in PLC/PRF/5 cells increased both the glycolysis and oxidative phosphorylation pathways, while the overexpression of NOX4 in SNU449 cells showed opposite effects. A detailed transcriptomic and metabolomic analysis indicated that NOX4 could be regulating fatty acid metabolism. We found differences in gene expression related to fatty acid transport, oxidation and de novo synthesis, as well in the amount of monoacylglycerol, diacylglycerol and carnitine intermediates, which indicate an inverse correlation between the expression of NOX4 and the cell capacity to use fatty acids. Silencing NOX4 induced changes in the amount and dynamics of the mitochondria, increase in the protein levels of complex IV and V and higher ATP levels. Preliminary results indicate that NOX4 regulates c-Myc, which could mediate the changes observed.
Conclusion: The liver tumor suppressor functions of NOX4 could be explained through its effects on HCC cell lipid metabolism.

AS129

Crucial role of beta-arrestin-2 in linking fibrogenesis and cancer

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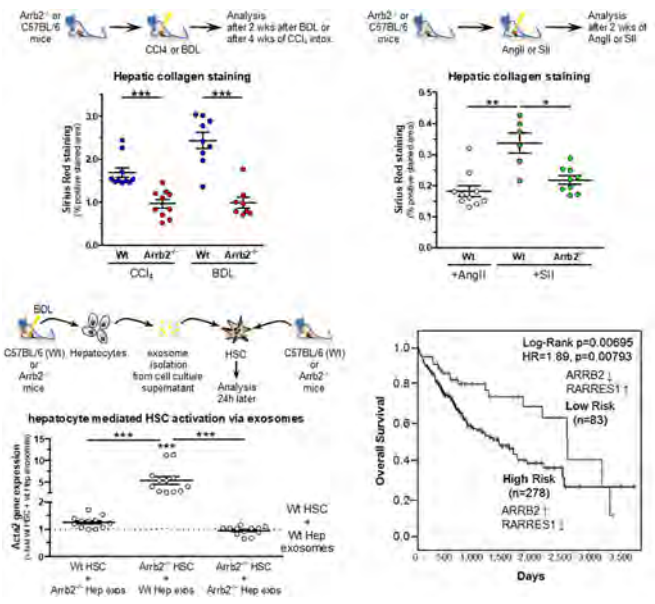
Background and Aims: Beta-arrestin-2 (ARRB2) is a regulator of the G protein-coupled receptors, such as the profibrotic Angiotensin II type 1 receptor (AGTR1), redirecting signalling to G protein-independent pathways. Their role in liver fibrosis, cancer and the transition from fibrosis to cancer are not fully understood and were investigated in this study.
Method: Fibrosis was induced in Arrb2-deficient and wildtype (Wt) mice using bile duct ligation (BDL) or carbon tetrachloride (CCl_4). AGTR1 was stimulated either G protein-dependent by angiotensin II administration or by the modified peptide [Ser(1), Ile(4), Ile(8)]-angiotensin II to selectively activate ARRB2 downstream of AGTR1. Fibrosis and HSC activation were investigated *in vivo* by gene and protein expression/histological staining. Crosstalk between primary murine hepatic stellate cells (HSC) and hepatocytes was analysed *in vitro*. Gene array analyses identified mediators of ARRB2-dependent signalling in primary human HSC. Findings in experimental liver fibrosis and cancer were confirmed in human tissue and hepatic cells (hepatocytes, HSC, HCC). Additionally, external validation was performed *in silico* using Geo-database, Oncomine and SurvExpress.
Results: ARRB2 is increased in human and experimental liver cirrhosis, mainly in activated HSC and injured hepatocytes. In turn, ARRB2-defiency decreases fibrosis and HSC activation *in vivo*. Interestingly, ARRB2-loaded exosomes released from injured Wt

hepatocytes are able to activate ARRB2-deficient HSC, while ARRB2-deficient exosomes had no effect in Wt HSC. Transcriptome analysis of human primary HSC revealed that ARRB2 induces retinoic acid receptor responder 1 (RARRES1). RARRES1 correlates with profibrotic factors, such as collagen 1, alpha-smooth muscle actin and transforming growth factor beta expression. On the other hand RARRES1 is a tumor suppressor. Release of ARRB2-positive exosomes from injured hepatocytes leads to RARRES1 downregulation in these hepatocytes. Decreased RARRES1 was also found in HCC cell lines and human tissue, while ARRB2 and RARRES1 were upregulated in surrounding cirrhotic peritumor tissue. In HCC, upregulation of ARRB2 and downregulation of RARRES1 could be confirmed in large human series using external validation.



Conclusion: Chronic liver injury leads to release pf ARRB2-loaded exosomes by hepatocytes. These exosomes are taken up by HSC and induce fibrosis. ARRB2 regulates RARRES1 and may induce pre-malignant transformation.

AS130

Inhibition of protein phosphatase 1b protects against lipotoxicity in liver progenitor oval cells

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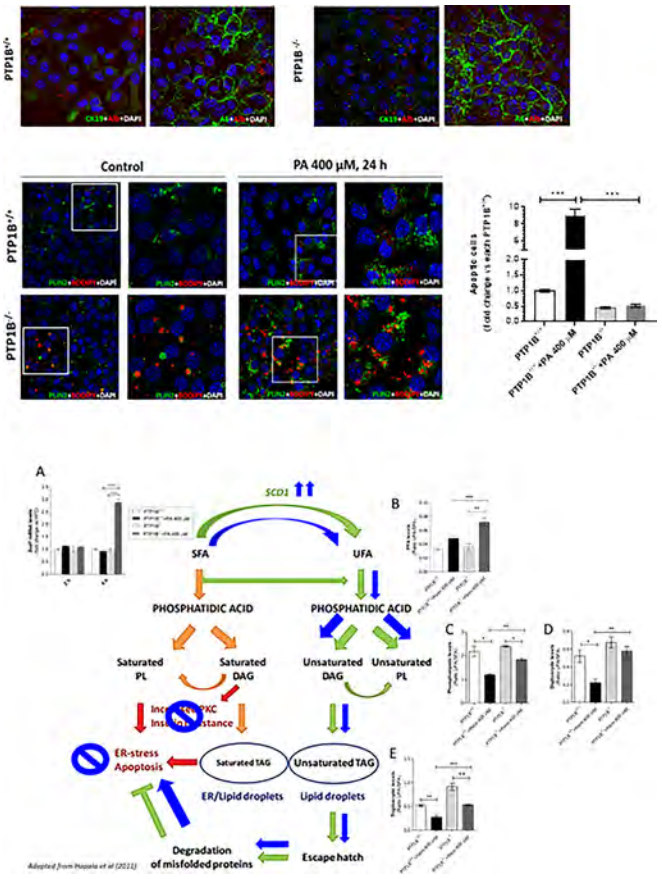
Background and Aims: Oval cells are progenitor cells with an emerging role in liver regenerative responses by their differentiation capacity. However, the characterization of their susceptibility to lipotoxicity in the context of obesity-associated non-alcoholic fatty liver disease is unknown. Inhibition of protein tyrosine phosphatase 1B (PTP1B) is a promising pharmacological strategy against insulin resistance and obesity. Also, PTP1B deficiency protects against acute and chronic hepatocyte damage. On that basis, we analyzed the susceptibility of oval cells with or without PTP1B to lipotoxicity and the molecular mechanisms involved.

Method: Oval cells from PTP1B$^{+/+}$ and PTP1B$^{-/-}$ mice were isolated, cultured and characterized. For lipotoxicity studies, oval cells were treated with palmitic acid (PA) for different time-periods, after which unfolded protein response (UPR) and autophagy/apoptosis markers were analyzed. A lipidomic study was conducted to characterize the accumulation of lipid species upon PA stimulation in PTP1B$^{+/+}$ and PTP1B$^{-/-}$ oval cells.



Results: Treatment with PA for 24 h induced apoptotic cell death in PTP1B$^{+/+}$ oval cells in parallel to a blockade of the autophagy flux. This lipotoxic effect was absent in PTP1B$^{-/-}$ cells that accumulated lipid droplets upon PA treatment and presented elevated levels of UPR-sensitive mediators, AMPK phosphorylation and sirtuin 1. These effects were also found in PTP1B silenced wild-type oval cells. Moreover, PA-treated PTP1B$^{-/-}$ oval cells showed an enhanced anti-oxidant response including nuclear factor erythroid 2-related factor nuclear translocation. Lipidomics revealed that upon PA treatment PTP1B$^{-/-}$ oval cells present elevations in stearoyl CoA desaturase 1 (Scd1) mRNA and higher unsaturated/saturated fatty acids after PA stimulation either free or incorporated into triacylglicerides, diacylglicerides and phospholipids. Blockade of autophagy flux in PTP1B$^{-/-}$ cells inhibited lipid droplet formation and restored lipoapoptosis.

Conclusion: Our results revealed that liver oval cells are susceptible to lipotoxicity, an effect mediated at least in part by the induction of oxidative stress. PTP1B deficiency protects against lipotoxic cell death by mechanisms including enhancement of antioxidant defence and a major capacity to generated unsaturated lipid species stored in lipid droplets, suggesting a potential benefit in cellular regenerative therapies against NAFLD. This effects are likely mediated by autophagy-derived energy suppliers.

AS131

The splicing regulator SLU7 is required for DNMT1 protein stability and DNA methylation maintenance

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Background and Aims: We have recently demonstrated that the splicing regulator SLU7 is essential for the survival of transformed cells of different origin including human HCC cells. In addition, SLU7 is required for securing normal liver regeneration after partial hepatectomy. Common to both scenarios is the increased cell proliferation. Indeed, we have identified SLU7 as a key mediator of cell cycle progression and genome stability. DNA methyltransferase 1 (DNMT1) is responsible for the maintenance of DNA methylation during cell division. DNA methylation regulates tissue-specific gene transcription in collaboration with other epigenetic regulators, affecting numerous cellular processes. Moreover, recent advances demonstrate that DNA methylation can influence alternative splicing. Based on this background, we aim to study the crosstalk between the splicing factor SLU7 and DNA methylation.
Method: SLU7 and DNMT1 expression were knocked-down in a large panel of human cancer cell lines of different origin (HCC cell lines PLC/PRF/5 and HepG2, colorectal carcinoma cell line HCT-116 and non-small cell lung cancer cell line H358, among others) and their reciprocal expression was determined by both qPCR and Western blot analysis. Global DNA methylation, gene-specific promoter methylation and the mechanism involved in this crosstalk were determined by different approaches. Finally, studies were performed in wild-type and SLU7 knocked down mice.
Results: Knock-down of DNMT1 enhanced SLU7 expression. Strikingly, SLU7 knock-down led to reduced DNMT1 abundance in proliferating normal and cancer cells, but does not affects its gene transcription levels. This DNMT1 depletion in SLU7 silenced cells was associated with global DNA hypomethylation and the re-expression of methylation silenced genes. Mechanistically, co-immunoprecipitation assays revealed that SLU7 and DNMT1 directly interact. Importantly, we found that this regulation also occurred in vivo and that SLU7 was required for DNMT1 expression after partial hepatectomy.
Conclusion: Our results demonstrate an absolute SLU7 requirement for DNMT1 protein stability unraveling an unknown connection between a splicing factor and epigenetic regulation. Deciphering into the mechanisms that control cell proliferation may contribute to develop new therapeutic strategies.

AS132

Scalable small molecule derived mini-liver organoids from human pluripotent stem cells

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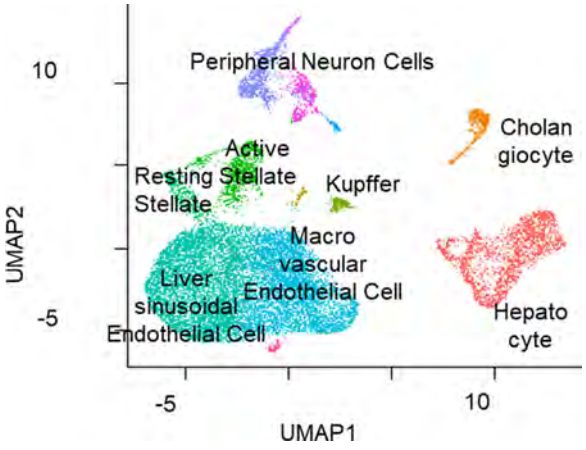
Background and Aims: A major limitation of human pluripotent stem cell derived cell-based products is the inability to adequately recapitulate human development in a 2 dimensional (2D) in vitro context. The lack of physiologically relevant cell culture systems greatly hampers both the maturity and functional aspects of nearly all stem cell derived cell types. This is especially true for the hepatic lineage derived from human pluripotent stem cells. Recently, a number of groups have strove to move away from traditional 2D tissue culture paradigms to more physiologically relevant 3 dimensional (3D) systems. The formation of organoid based differentiation protocols have been reported for cell types representative of the three germ layers, including hepatic organoids. However currently available methods suffer from a number of drawbacks, including a high reliance on extracellular matrices (ECM), such as Matrigel, to support cystic organoid growth, and the use of costly growth factors both being a hurdle for scaling. Additionally, current 3D hepatic organoids are generally a single cell type, i.e. hepatocytes or cholangiocytes, thus rendering them less physiologically relevant as compared to native tissue.



Method: To address these shortcomings, we have translated our recently reported small molecule driven hepatocyte differentiation protocol from 2D to 3D. Importantly the present work requires no expensive infrastructure, is ECM independent and can be easily scaled to produce massive amounts of 3D "mini-liver" organoids.
Results: The organoids showed enhanced functional attributes when compared to 2D controls. Importantly, the organoids maintained key hepatic functions long term in culture as compared to their 2D counterparts. Single cell RNA sequencing (21,000 cells, figure 1), proteomics and extensive profiling via immunochemistry revealed the formation of liver organoids containing the major cell types of the native liver including parenchymal cells, hepatocytes and cholangiocytes, and non-parenchymal cell types including hepatic stellate cells, liver sinusoidal endothelial cells, vasculature structures, and kupffer cells.
Conclusion: This protocol serves as an inexpensive and simple method to produce massive quantities of liver like tissue with enhanced function and maturity a pre-requisite for a myriad of applications including cellular therapy, tissue engineering, pharmaceutical drug toxicity assessment, disease modelling, and basic developmental research.

NAFLD – Experimental

AS133

Myosteatosis is associated with early NASH in the context of obesity and metabolic syndrome

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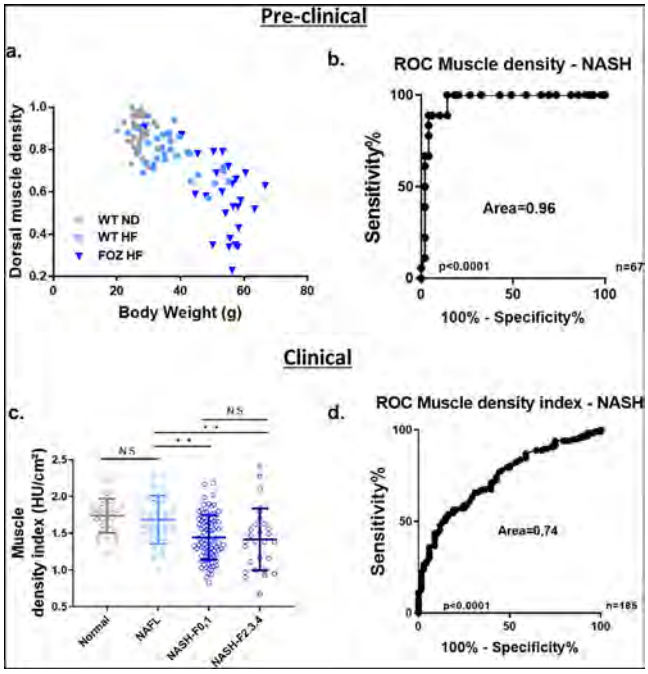
Background and Aims: A substantial body of literature supports that a low muscle mass, low strength or a higher muscle fatty infiltration are associated with NAFLD presence and severity. Here, we investigated the muscle compartment in NAFLD models and a human cohort to evaluate muscle changes in correlation with liver disease progression.

Method: For over 34 weeks, we followed WT mice fed a standard chow as controls (Ctl), WT mice fed a high fat (HF) diet (60% fat) as a model of simple steatosis (WT HF) and foz/foz mice fed a HF diet as a model of progressive NASH (FOZ HF). We developed and validated a novel preclinical micro-Computed Tomography (micro-CT) based methodology to prospectively study skeletal muscle mass and fatty infiltration in muscle and liver in a high-throughput and non-invasive manner. We used CT to measure skeletal mass and fatty infiltration retrospectively in a large cohort of 197 morbidly obese patients with biopsy-based liver histology (62.4%, 19.7% and 17.2% had respectively NASH, NAFL and normal liver histology).

Results: In animals with NASH, muscle mass dissociated from body weight gain and relative decrease in muscle mass was associated with severe loss of muscle strength from 12 week on. Myosteatosis was the earliest muscular change as reflected by a significantly lower muscle density in FOZ HF as early as 4 week (0.79 ± 0.02) when compared to Ctl (0.91 ± 0.02). Myosteatosis severity was strongly correlated with NAS score ($r = -0.87$, $n = 67$, $p < 0.001$), irrespectively of the time point studied, and could not be explained by the higher body weight of foz/foz (Fig. 1a). Myosteatosis powerfully discriminated NASH from non NASH-NAFL or normal liver (AUROC = 0.96, $p < 0.001$) in this model (Fig. 1b). In a large population of 185 morbidly obese patients, CT-derived myosteatosis identified patients with biopsy proven NASH amongst those with uncomplicated steatosis and normal liver histology (Fig. 1-c,d), independently of possible confounding factors and outperforming classical biomarkers such as FIB4, NFS and CK18 (AUROC = 0.57, 0.52 and 0.55 respectively). Myosteatosis inclusion in a multivariate model returned an AUROC of 0.81 for NASH prediction ($p < 0.001$).



Conclusion: Taken together, our data support that myosteatosis, hepatocellular damage and inflammation develop synchronously with NASH onset, paving the way for the exploitation of myosteatosis as a non-invasive marker of NASH and suggesting a muscle-liver reciprocal cross-talk during liver disease progression.

AS134

Vitamin D3 up-regulated protein 1 attenuates non-alcoholic steatohepatitis by regulating AMPK/mTORC1/TFEB-mediated autophagy

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is caused by abnormal lipid metabolism and can progress to non-alcoholic steatohepatitis (NASH). Recent studies have demonstrated hepatic autophagy being impaired in NASH patients, but its underlying mechanisms remains unclear. Here, we investigated the role and regulatory mechanism of vitamin D3 up-regulated protein 1 (VDUP1), a key mediator of cellular stress responses, in the pathogenesis of NASH.

Method: Human liver biopsies from normal healthy donors and NASH patients were quantitatively evaluated by immunohistochemistry for VDUP1, LC3B, and p62/SQSTM1. A control diet or a methionine- and choline-deficient (MCD) diet was fed to wild-type (WT) and VDUP1 knockout (KO) mice to induce nutritional steatohepatitis for 4 weeks with or without rapamycin treatment (5 mg/kg/d). For *in vitro* experiment, isolated primary WT and VDUP1-KO hepatocytes were treated with AICAR (500 μM) for 6 hours and starved.

Results: Hepatic VDUP1 expression was dramatically up-regulated in NASH patients compared with healthy controls. VDUP1 expression was positively correlated with steatosis ($r = 0.6420$, $p = 0.0099$),

hepatocellular ballooning (r = 0.6624, p = 0.0071), lobular inflammation (r = 0.5160, p = 0.0492), and NAFLD activity score (NAS; r = 0.6894, p = 0.0045). The number of LC3B puncta, a well-known marker of autophagosomes, was significantly lower in NASH patients compared with normal controls, while the expression of p62/SQSTM1, a protein specifically degraded by autophagy, was increased. VDUP1 KO mice showed severe hepatic steatosis, inflammation, and fibrosis, accompanied by impaired autophagy compared to WT mice after MCD-diet feeding. VDUP1 directly interacted with phospho adenosine monophosphate-activated protein kinase (AMPK), leading to inactivation of mTOR complex 1 (mTORC1) and nuclear translocation of transcription factor EB (TFEB), which in turn promoted autophagy. AMPK activation with AICAR stimulated autophagy with mTORC1 inhibition and nuclear TFEB translocation in VDUP1-KO hepatocytes. Finally, inhibition of mTORC1 with rapamycin ameliorated MCD-diet induced steatosis, inflammation, and fibrosis with activation of TFEB and induced autophagy in VDUP1 KO mice.
Conclusion: This study suggests that up-regulation of hepatic VDUP1 serves as a protective mechanism that ameliorates NASH by promoting AMPK/mTORC1/TFEB-mediated autophagy. A possible therapeutic strategy for NASH may be to target VDUP1.

AS135

Inhibition of ? 24-dehydrocholesterol reductase ameliorates non-alcoholic steatohepatitis in mice

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Background and Aims: Δ24-Dehydrocholesterol reductase (DHCR24) is a crucial terminal enzyme in cholesterol biosynthesis converting the ultimate intermediate desmosterol into cholesterol. Desmosterol is an endogenous liver X receptor (LXR) ligand with anti-inflammatory properties and reduces cholesterol and fatty acid biosynthesis by suppressing signaling via sterol regulatory element binding protein 1c. We hypothesized that increasing desmosterol levels obtained via inhibiting DHCR24 reduces hepatic steatosis and inflammation, the two most important hallmarks of nonalcoholic steatohepatitis (NASH). Thus, by using the novel DHCR24 inhibitor SH42, characterized by high potency and selectivity, we aimed to investigate the therapeutic effects of DHCR24 inhibition on NASH development.
Method: *APOE*3-Leiden.CETP* mice, a well-established translational model for lipoprotein metabolism that develops diet-induced human-like NASH characteristics, were fed a high fat and cholesterol diet (HFCD) with or without simultaneous SH42 treatment. After 8 weeks, liver steatosis and inflammation were assessed. Lipidomics, lipid mediators and cholesterol biosynthesis analyses were carried out on plasma and liver.
Results: DHCR24 inhibition via SH42 treatment markedly increased plasma desmosterol levels (+5,600%), without influencing food intake nor affecting body weight and body composition during the whole time-frame of intervention. SH42 decreased plasma cholesterol esters (−24%) and fatty acid (−19%) levels whilst not affecting diacylglycerol (DAG) and triacylglycerol (TAG) levels. Notably, SH42 largely increased plasma 19,20-epoxydocosapentaenoic acid (19,20-EpDPA) levels (+210%), a well described and potent anti-inflammatory/pro-resolving lipid mediator. In the liver, SH42 reduced the neutral lipid content, namely DAG (−21%), TAG (−38%) and cholesteryl esters (−26%). Moreover, liver histological assessment showed that SH42 prevented HFCD-induced hepatic steatosis, inflammation, ballooning and crown-like structure formation. Flow cytometry analysis also showed that SH42 reduced the number of F4/80^{low} CD11b^{high} Ly6c^{high} infiltrating monocytes in the liver.
Conclusion: Inhibition of DHCR24 by SH42 increases plasma desmosterol, accompanied by reduction of hepatic steatosis, inflammation and damage. We anticipate that DHCR24 inhibition is a potential novel therapeutic strategy for the treatment of NASH by killing two birds with one stone, i.e. inflammation as well as hepatic fat accumulation.

AS136

The bile acid derivative norursodeoxycholic acid affects fatty-liver associated anhedonia and anxiety in mice

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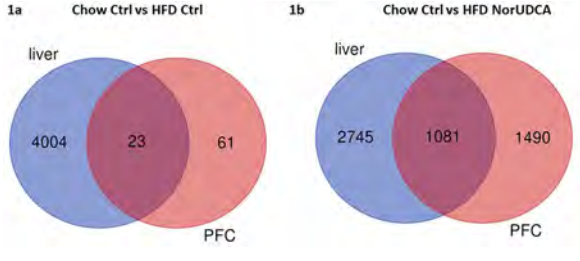
Background and Aims: Chronic liver diseases, such as non-alcoholic fatty liver disease, and metabolic conditions like obesity are associated with behavioral disorders like anxiety and depression, but the underlying pathophysiology is not well understood. We aimed to deepen the understanding of the interaction of high-fat diet induced liver disease and obesity with brain structures involved in emotion processing. To evaluate the potential of targeting a putative shared underlying disease mechanism, we tested the effect of chronic NorUrsodeoxycholic acid (NorUDCA) on anxiety and depression-like behavior in mice.
Method: Male C57BL/6J mice received either chow (A04, Safe Diets, France) or high-fat-diet (HFD, 36% fat from butter, HF260, Safe Diets, France) ±0.5% NorUDCA for 39 weeks. Starting at week 8, all groups were tested in standard behavioral assays while feeding continued. Functional magnetic resonance imaging (fMRI) of the brain was used in stressed and unstressed conditions with blood-oxigen-level-dependent (BOLD) imaging as a proxy for neuronal activity. We used liquid-chromatography based mass spectral analysis for the measurement of neurotransmitter and bile acid species. mRNA was extracted from livers and brains (n = 5 per group). A Tn5 enzyme based RNA-seq library prep was performed and underwent Ilumina seq. Genes were ranked by log2FC and a p-adjusted threshold of <0.05 was applied. Ingenuity Pathway Analysis (IPA, Quiagen) and PANTHER were used for further analysis.
Results: Chronic NorUDCA treatment in mice which received a high-fat diet reduced food consumption and body weight as well as anhedonia, fear and anxiety. Mass spectrometry showed that NorUDCA is present in the brain tissue of NorUDCA-treated mice, and that NorUDCA treatment also alters neurotransmitter makeup. Using transcriptome analysis, 23 differentially expressed (DE) genes were induced by HFD in both the liver and the prefrontal cortex (PFC) (Fig. 1a), and 1081 DE genes were induced in both the liver and PFC in the HFD NorUDCA group when compared to Chow Ctrl group (Fig. 1b).



Conclusion: This study shows for the first time an effect of a bile acid derivative on the brain to control HFD associated stress, anxiety and depression as well as ameliorating HFD induced- fatty liver disease in mice, deepening our understanding of the shared pathophysiology and treatment of these conditions.

AS137

Effect of the hepatic extracellular vesicles in inflammation-associated insulin resistance in non-alcoholic fatty liver disease

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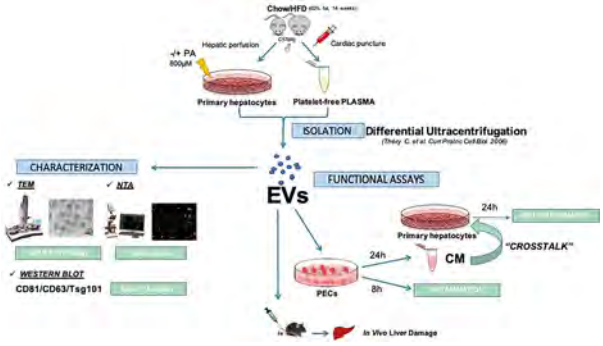
Background and Aims: Cell-to-cell communication by extracellular vesicles (EVs) is an emerging issue in non-alcoholic fatty liver disease (NAFLD). However, the EVs role in the interactome within liver cells remains uncertain. Thus, we aimed to analyze EVs secretion in hepatocytes under NAFLD conditions, their impact on macrophages inflammation and, ultimately, in hepatocytes insulin signaling.
Methods: C57Bl6j male mice were fed chow (control) or high-fat diet (HFD) for 14 weeks. Exosome-enriched fraction (Exos) was isolated by differential ultracentrifugation from: *1)* hepatocytes from chow-fed mice without (Exo^{Ch}) or with palmitic acid treatment (PA) (Exo^{PA}), *2)* hepatocytes from HFD-fed mice (Exo^{HFD}), *3)* plasma from chow- (Circ- Exo^{Ch}) or HFD-fed mice (Circ-Exo^{HFD}). Exos were characterized by Western-blot, Transmission Electron Microscopy and Nanoparticle Tracking Analysis. Mouse peritoneal macrophages (PECs) were stimulated for 8 hours with different Exos fractions and inflammatory responses were assessed by RT-qPCR and immunofluorescence. PKH67-stained Exos were added to PECs to monitor their internalization. Hepatocytes were incubated for 24 hours with conditioned medium (CM) from Exos-treated PECs to examine insulin signaling. C57Bl6j mice were injected intravenously with hepatocyte-derived Exos to analyze *in vivo* effects (**graphical abstract on Figure**).



Results: The release of Exo^{PA}, Exo^{HFD} and Circ-Exo^{HFD} was increased compared to Exo^{Ch} and Circ-Exo^{Ch}. Exos were internalized by PECs through the endosomal pathway and both Exo^{PA} and Exo^{HFD} triggered proinflammatory responses such as nuclear NF-kappaB translocation and elevations in Il6 and Il1beta mRNAs. Moreover, insulin resistance was induced in hepatocytes incubated with CM from PECs that received Exo^{PA}, Exo^{HFD} and Circ-Exo^{HFD}. Livers from mice injected with Exo^{PA} and $Exo^{HFD,}$ but not Exo^{Ch}, showed increased stress kinases signaling and NF-kappaB nuclear translocation at 1 h post-injection. Furthermore, hepatocyte insulin resistance was found when mice were treated for 24 hours with Exo^{PA} and $Exo^{HF}D$.
Conclusion: Our results identified a novel molecular mechanism in the interactome hepatocyte-macrophage-hepatocyte where both Exos from hepatocytes under NAFLD conditions and from plasma from HFD-fed mice induced insulin resistance through macrophages inflammatory responses. The study of the cargo from hepatocyte-derived Exos could provide new mechanistic insights on this interactome during NAFLD.

AS138

Alterations in bile acids and TGR5 activation in non-alcoholic steatohepatitis

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Background and Aims: Bile acids (BA) modulate lipid and glucose homeostasis, energy expenditure, inflammatory tone and fibrosis through Farnesoid X receptor (FXR) and G-protein-coupled receptor (TGR5) signaling. Altered BA sensing and signaling might thus contribute to NASH pathogenesis. In humans, BA analysis is restricted to systemic blood and feces and reflects BA that escaped hepatic uptake and intestinal reabsorption, respectively, and thereby does not reflect the enterohepatic BA pool. Studying BA in mice enables the assessment of BA profile in bile and portal blood. Here, we aimed to determine BA profile in a mouse model of NASH.
Method: We studied foz/foz mice (FOZ) and WT mice fed a HFD for 12 weeks as a model of NASH (NAS $\geq$ 6) and of simple steatosis (NAS $\leq$1), respectively. Portal blood, bile, feces and tissues were sampled after 12 h fasting and 4 h refeeding. BA profiling was established by LC-MS/MS. To test TGR5 activation, HEK293 T cells overexpressing TGR5 and a CRE luciferase reporter were exposed to portal plasma of FOZ and WT mice. Bile flow was assessed by cannulation of the gallbladder.
Results: Total BA concentration in bile was similar in both groups but the proportion of primary BA was higher and that of secondary BA was lower in FOZ (83%/17%) than in WT mice (62%/38%) (Figure, left). As supported by equal bile flow and BA concentration, the amount of BA secreted by the liver is similar in FOZ and WT mice. Increased expression of Cyp7a1 and Cyp8b1 in FOZ mice supports increased primary BA synthesis through the main classical pathway. Total BA concentration as well as the absolute and the relative concentration of secondary BA was lower in the portal blood of FOZ than in WT mice (Figure, right). This could be explained by a defective transformation of primary to secondary BA by the gut microbiota or by reduced intestinal BA reabsorption. However, similar fecal BA amount does not support the later hypothesis. Overall, altered BA profile in FOZ corresponded to low TGR5 agonist species in portal blood and in accordance, in a TGR5 reporter assay, the plasma of FOZ mice was 3.4-fold less effective in activating TGR5 than the plasma of WT mice.

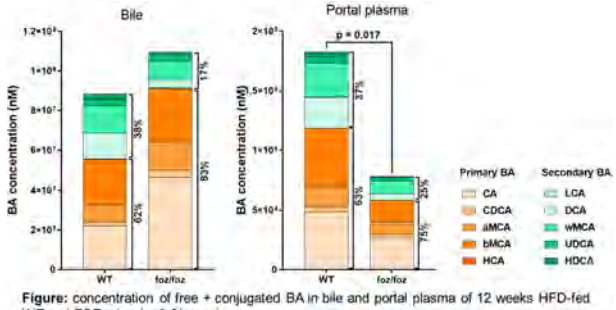

Figure: concentration of free + conjugated BA in bile and portal plasma of 12 weeks HFD-fed WT and FOZ mice (n=6-8/group).

Conclusion: Deep alteration in BA pool, likely due to reduced transformation of primary to secondary BA by the gut microbiota, results in reduction of TGR5 ligands in the portal blood that could contribute to NASH pathogenesis in this experimental model.

SAT031

Genome-wide in vivo functional genetic screen to identify novel modulators of non-alcoholic fatty liver disease

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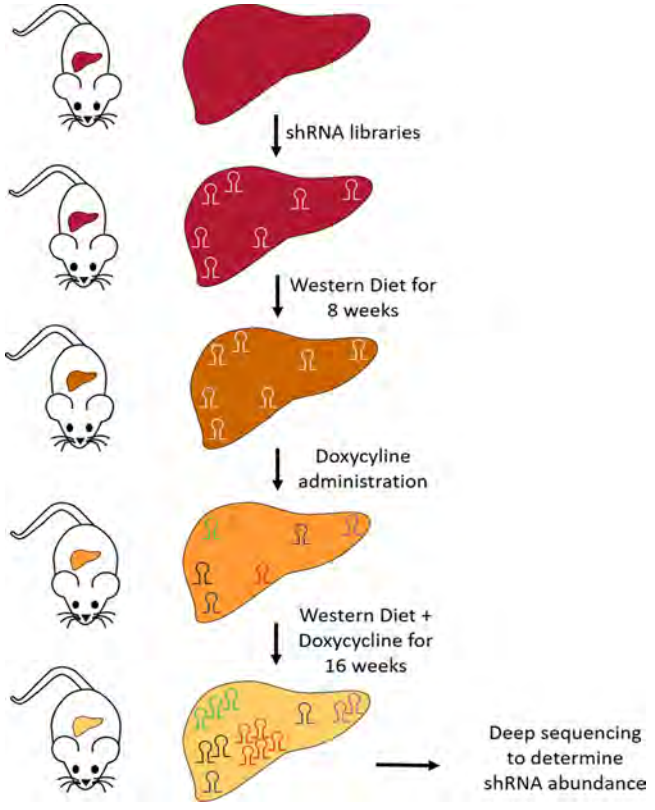
Background and Aims: With a global prevalence of 25.2%, Non-Alcoholic Fatty Liver Disease (NAFLD) is the leading cause of chronic liver disease requiring transplantation worldwide. Despite this, NAFLD continues to be an underdiagnosed disease with no current approved treatment. This is primarily due to lack of understanding of the mechanisms underlying disease development and progression. To address this, we performed a genome-wide *in vivo* functional genetic screen to identify novel regulators of NAFLD. Our study aims to be the first-of-its kind to unravel the molecular basis of NAFLD with the hope of developing innovative therapeutics to address the imminent healthcare burden of this dreaded disease.



Method: RNA interference technology has transformed loss-of-function genetics. We adopted this technology to carry out a functional genetic screen to identify novel gene targets in NAFLD. shERWOOD-UltramiR shRNA library targeting the whole mouse genome was shuttled into the pT-T3GEPIR transposon-based plasmids to develop an inducible system. Hydrodynamic injection was used to stably deliver these along with sleeping beauty transposase to the hepatocytes of C57Bl6J mice. To recapitulate the fatty liver phenotype, mice were fed "Western Diet" supplemented with high fructose. Following 8 weeks of treatment, the first signs of fatty liver were observed and doxycycline was added to induce expression of the shRNA libraries. These mice were fed for another 16 weeks during which they mimicked slow disease progression similar to what is seen in humans, with patterns of obesity, steatosis, inflammation and fibrosis. The underlying idea of the screen is that shRNAs that give the hepatocyte an advantage in the detrimental environment, will increase in abundance over time. In contrast, if the knockdown is a disadvantage for the hepatocyte, the shRNA will deplete over time. If a shRNA has no influence, its abundance should not change in the pool. Illumina-based deep sequencing was used to determine the abundance of the shRNAs. Since this system includes several variables, only shRNAs that are reliably enriched or depleted (95% confidence interval with a 4-fold change) will be selected for further validation. Additionally, our results will be compared with clinical data from human NAFLD patient tissues as well as patient-derived organoids to ensure translation of our findings in human disease.

Results: Our preliminary results have identified several novel shRNAs that were enriched or depleted during the progression of NAFLD thereby conferring a negative or positive effect on the regenerative capacity of hepatocytes.

Conclusion: A genome-scale screen in a disease like NAFLD where there is limited understanding of the underlying molecular mechanism guarantees the uncovering of new insights that will prove useful in the development of novel therapeutics.

Liver fibrosis

AS139

Blocking MAIT cell activation accelerates liver fibrosis regression

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Background and Aims: Mucosal-Associated Invariant T (MAIT) cells are non-conventional T cells that are restricted by the non-classical MHC-1b molecule MR1 and display altered functions during chronic liver diseases. We have demonstrated the pro-inflammatory and profibrogenic properties of MAIT cells in the liver. Here, we investigated whether targeting MAIT cells to block their activation may impact on fibrosis regression and the mechanisms involved.

Method: Liver fibrosis was induced by repeated injection of carbon tetrachloride (CCl_4) in (i) C57BL6/J WT mice, (ii) MAIT cell-enriched *Mr1+* RORγt-Gfp^{TG}B6-MAIT^{CAST} (CastMr1^{+}) and (iii) MAIT cell-deficient *Mr1*-deficient B6-MAIT^{CAST} (Mr1$^{-/-}$) mice. For fibrosis regression, CCl_4 injections were discontinued and mice were daily administered with either Acetyl-6-formylpterin (Ac-6-FP), an inhibitor of MAIT cell activation or an anti-MR1 blocking antibody for 4 days. Frequency and phenotype of hepatic MAIT cells were analyzed by multi-color flow cytometry, defined as MR1:5-OP-RU tetramer-positive (MR1tet^{+}) cells. Pro-inflammatory (Ly-6C^{high}) and restorative (Ly-6C^{low}) macrophages were sorted from CCl_4-exposed mice treated with Ac-6-FP after the last injection of CCl_4, and their signature analyzed by RNA sequencing.

Results: Liver fibrosis was exacerbated in CastMr1^{+} as compared to Mr1$^{-/-}$ counterparts, and fibrosis remained elevated 4 days after the last CCl_4 injection. Compared to vehicle-treated animals, CCl_4-exposed CastMr1^{+} mice daily injected with Ac-6-FP showed accelerated fibrosis regression, as reflected by lower sirius red and α-SMA staining areas 4 day after the last CCl_4 injection. Similar findings were obtained when injecting an anti-MR1 antibody. Interestingly, acceleration of fibrosis regression by Ac-6-FP was no longer observed when macrophages were depleted using clodronate liposome. Flow cytometry analysis of hepatic leukocytes showed that Ac-6-FP promoted a decrease in Ly-6C^{high} and an increase in Ly-6C^{low} macrophage frequency. Furthermore, RNA sequencing analysis of

macrophage signature showed differential metabolic reprogramming of Ly-6C^{high} and Ly-6C^{low} by Ac-6-FP.
Conclusion: Blocking MAIT cell activation accelerates liver fibrosis regression, demonstrating that targeting MAIT cells may offer new perspectives for antifibrogenic therapy.

AS140
HDL cholesterol blocks NF-kB activation and M1 macrophages transformation thus reducing hepatic fibrosis in mice with selective intestinal LXR-alpha activation
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Background and Aims: Liver fibrosis is the result of the wound healing response during chronic liver injury. HDL cholesterol (HDL) possesses anti-inflammatory and anti-oxidant effects in atherosclerotic plaque macrophages but its role in hepatic fibrosis is unknown. HDL metabolism is regulated by LXR but its hepatic activation is hampered by major side effects such as hepatic steatosis. Thus, aim of the present study was to evaluate whether selective intestinal activation of LXR could increase HDL levels and reduce hepatic fibrosis without the side effects on hepatic activation.
Method: Mice with intestinal constitutive LXRα activation (iVP16-LXRα) were exposed to intraperitoneal injection of carbon tetrachloride (CCl4) for 8 weeks.
Results: Compared to control iVP16 mice (iVP16), iVP16-LXRα showed reduced hepatic macrophage infiltration and a shift toward a M2 phenotype determined by arginine-1 (ARG1) expression and of the number of M2 macrophages co-stained with CD68 (pan-macrophage marker) and CD206 (M2 marker). In the liver of iVP16-LXRα, reduced gene expression of NF-kB was observed together with decreased p65 subunit immunostaining associated with lower expression of NF-kB downstream pro-inflammatory genes (TNFα, IL1β, IL6). Furthermore, gut LXRα activation decreased hepatic oxidative stress (by malonildialdehyde quantification and expression of the superoxide-generating NOX1 and 2) and increased mRNA levels of the defensive mechanism toward oxidative stress heme oxygenase-1 (HO-1). Decreased hepatic inflammation and oxidative stress lead to reduced fibrosis (by morphometry for Sirius Red and α-smooth muscle actin, and by hydroxyproline quantification), and fibrogenesis (by TGFβ and TIMP1 gene expression). Intestinal LXRα activation increased HDL synthesis in the gut, shown by gene expression of intestinal ATP-binding cassette transporter 1 (ABCA1), associated with higher levels of circulating HDL and of its hepatic receptor SIRB1. Correspondingly, in LPS-stimulated Kupffer cells (KC), HDL blocked the shift to M1 phenotype by ARG1 expression and decreased pro-inflammatory gene expression (TNFα, IL1β, IL6) by blocking LPS-induced NF-kB nuclear translocation. We thus hypothesized that activated macrophages could signal hepatocytes via TNFα. In fact, in TNFα–incubated hepatocytes, HDL again blocked NF-kB nuclear translocation together with expression of NOX1, IL1β, and IL6 expression while increasing HO-1 mRNA levels. These effects were not associated with hepatic steatosis development in vivo as shown by decreased hepatic SREBP1-c expression and triglyceride levels in iVP16-LXRα compared to iVP16.
Conclusion: Selective intestinal LXRα activation might represent a new target for the treatment of hepatic fibrosis, by increasing HDL circulating levels without the occurrence of the side effects related to hepatic LXR induction.

AS141
Toll-like receptor 4 signaling in bone marrow-derived macrophage promotes resolution of carbon tetrachloride-induced murine liver fibrosis
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Background and Aims: Liver cirrhosis is the result of favoured fibrogenesis over ineffective fibrosis resolution. The pro-fibrotic roles of macrophage and its crosstalk between hepatic stellate cells through pattern-recognition receptors during the inflammatory phase of liver fibrosis have been extensively studied, however, these processes are relatively unclear during fibrosis resolution. By focusing on the gut-liver axis, we aimed to clarify the possible role of toll-like receptor 4 (TLR4) signaling pathway in macrophages during fibrosis resolution.
Method: Age-matched wild-type (WT) B6 mice were intraperitoneously injected repetitively with carbon tetrachloride (CCl_4, 0.6 ml/g) for 4 weeks to induce liver fibrosis. After the last injection, mice were observed or manipulated at specific time points until 7 days, known as the spontaneous fibrosis resolution phase of this model. Levels of liver fibrosis were evaluated by histology and protein contents. Hepatic and bone marrow mononuclear cells, total in vivo matrix metalloproteinase (MMP) activity were studied by flow cytometry. During the fibrosis resolution phase, multiple antibiotics per os for gut sterilization, TAK-242 iv for selective inhibition of intracellular signaling of TLR4, and bone-marrow transplantation (BMT) of TLR4-knockout mice were also used. In vitro phagocytosis assay was used to study the matrix-degrading phenotype of macrophages.
Results: During the fibrosis resolution phase, the whole liver demonstrated significantly elevated expression of TLR4, but not TLR2, TLR6 or TLR9. Total in vivo MMP activity study revealed that CD11b-posiive macrophages were the principal producer of MMPs. TAK-242 administration significantly retarded fibrosis regression histologically, and depressed whole liver MMP12 expression ($p < 0.01$). Gut sterilization during the fibrosis resolution phase also significantly demonstrated the same phenotype as TLR4-inhibition by TAK-242, which implicated gut-liver axis might play a possible pro-fibrolytic role through TLR4 signaling. In the BMT experiments, TAK-242 administration significantly retarded fibrosis regression in TLR4- knockout mice with WT-BM transplanted ($p < 0.05$), but not in WT mice with TLR4-/- BM transplanted, which implicated TLR4 signaling in the BM-derived cells, but not in hepatic parenchymal cells, is crucial for fibrosis resolution. In the in vitro phagocytosis assay, the matrix degrading phenotypes of BM-derived macrophages, including down-expression of Ly6C and MMP12 expression, were both significantly depressed by in vitro TAK-242 administration ($p < 0.05$).
Conclusion: In CCl_4-induced murine liver fibrosis, TLR4 signaling in bone marrow-derived macrophages promotes fibrosis resolution through MMP12 production. TLR4 signaling in macrophages may be a potential therapeutic target for accelerating liver fibrolysis.

AS142
Macrophage cell-specific deletion of cathepsin d amplifies liver inflammation and fibrosis
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Background and Aims: Changes in proteolytic activity are essential to liver fibrosis development. Proteases control not only matrix turnover but also, the activation and repression of growth factors and

chemokines influencing disease progression. Beyond metalloproteases, our knowledge of the proteolytic enzymes contributing to liver fibrosis is limited. The importance of lysosomal protease cathepsin D (CtsD) in kidney fibrosis has been recently demonstrated but its role in liver fibrosis remains elusive. Thus, the aim of this study was to analyse CtsD cells-specific role during liver fibrosis.

Method: To study the cell-specific role of CtsD we generated two novel knock-out mouse strains by breeding LysMCre (macrophages) or AlbuminCre (hepatocytes) mice with CtsD floxed mice. CtsD cell-specific deletion was confirmed in primary isolated hepatocytes and peritoneal macrophages by PCR and WB. Fibrosis was established chronically by CCl_4 (0.5 µl/g) in $CtsD^{AlbCre+/+}$ and $CtsD^{AlbCre-/-}$ or $CtsD^{LysMCre+/+}$ and $CtsD^{LysMCre-/-}$. Liver damage was determined by serum ALT and H&E staining. Fibrotic and inflammatory genes were determined by real-time-PCR in total liver. CtsB, CtsD and α-SMA were determined by immunohistochemistry or WB.

Results: First we determined CtsD expression in WT after chronic CCl_4 challenge, demonstrating CtsD presence in hepatocytes and macrophages. CtsD cell-specific deletion was validated by protein expression (WB) and floxed allele recombination (PCR), using primary mouse hepatocytes and peritoneal macrophages from $CtsD^{AlbCre+/+}$ and $CtsD^{LysMCre+/+}$ respectively and in comparison, with their floxed counterparts. To note, cathepsin B expression remained unaffected in hepatocytes or macrophages from $CtsD^{AlbCre+/+}$ or $CtsD^{LysMCre+/+}$ respectively. Neither CtsD deletion in macrophages nor in hepatocytes affected liver damage after chronic CCl_4 administration. CtsD cell-specific deletion in macrophages, but not in hepatocytes, increased liver fibrosis as shown by an increase in Sirius red staining, alpha-SMA protein expression and increased hepatic alpha-SMA, TGF-beta and Col1A1 mRNA. Furthermore, inflammation was affected only in macrophage-CtsD deficient mice showing significant increase in CCL2, CCL3 and CCL4. Finally, lack of CtsD in macrophages during liver fibrosis resulted in an upregulation of MMPs, such as MMP7 and MMP13.

Conclusion: Specific deletion of CtsD in macrophages, but no in hepatocytes, triggers upregulation of inflammation and matrix remodeling, leading to an amplification of the fibrotic response.

AS143

Single cell RNA-seq of patient liver tissues uncover HRH2+/CLEC5a high/macro low macrophages as therapeutic target for the treatment of liver fibrosis and cancer prevention

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Background and Aims: Advanced liver fibrosis is a major risk factor for hepatocellular carcinoma (HCC). There are no approved anti-fibrotic therapies and compounds in clinical development only have shown unsatisfactory clinical efficacy. Applying a human cell-based model system for liver disease therapeutics discovery using a clinical prognostic liver signature as a read-out (cPLS system), we identified nizatidine, a histamine receptor H2 (HRH2) blocker, as a candidate compound for treatment of liver fibrosis and HCC chemoprevention.

Method: To decipher nizatidine's mechanism of action, we performed perturbation studies using the cPLS system followed by validation in two NASH-HCC animal models and patient-derived tissues. Using our recently developed single cell RNA-Seq (scRNA-Seq) pipeline (Aizarani et al. Nature 2019), we combined scRNA-Seq analyses of patient liver tissues with perturbation studies to uncover the liver cells targeted by nizatidine.

Results: Nizatidine markedly and significantly reduced liver fibrosis, inflammation and hepatocarcinogenesis in two complementary mouse and rat models for NASH-HCC, as shown by a decrease of the collagen proportionate area (CPA), α smooth muscle actin (αSMA) staining, quantitative analysis of hydroxyproline and expression of genes mediating fibrogenesis. Mechanistic studies uncovered the HRH2/cAMP/CREB pathway as a pan-etiology driver for progression of fibrotic liver disease and hepatocarcinogenesis. Single cell RNA-Seq of human liver tissue treated with nizatidine identified pro-inflammatory $HRH2^{+}$/$CLEC5A^{high}$/$MARCO^{low}$ liver macrophages as a nizatidine target. Gene-level analyses in patient liver-derived macrophages revealed that nizatidine decreases expression of chemoattractant and pro-inflammatory cytokines, corresponding to a decrease of neutrophil/monocyte infiltration and of liver inflammation observed in the NASH-HCC mouse model. Restoration of the expression of patient liver macrophage antigen presentation-related pathways combined with an increase of $CD8^{+}$ T cell recruitment in liver of nizatidine-treated animals suggest improvement of anti-cancer surveillance.

Conclusion: By improving liver fibrosis, inflammation and anti-cancer surveillance, HRH2 targeting compounds provide a therapeutic candidate approach for patients with advanced fibrosis at risk for HCC and will guide future optimization of refined HRH2-targeting liver disease therapies.

AS144

PLN-74809, a clinical-stage, dual alphaVbeta6/alphaVbeta1 integrin inhibitor, reduces fibrosis in a preclinical model of biliary fibrosis and precision-cut liver slices from primary sclerosing cholangitis and primary biliary cholangitis patients

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Background and Aims: Integrins $\alpha_V\beta_6$ and $\alpha_V\beta_1$ are heterodimeric cell-surface proteins that bind to and activate latent transforming growth factor (TGF)-β, a key driver of fibrosis. In primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC), integrins $\alpha_V\beta_6$ and $\alpha_V\beta_1$ are thought to play a role in the development and propagation of fibrosis through the activation of TGF-β by cholangiocytes and stellate cells, respectively. PLN-74809 is an investigational, oral, dual-selective inhibitor of $\alpha_V\beta_6$ and $\alpha_V\beta_1$ that is currently in clinical studies. The study aims were 1) to test the ability of PLN-74809 and PLN-75068, a related dual-selective inhibitor, to block biliary fibrosis through inhibition of integrin-mediated TGF-β activation and 2) to evaluate safety and pharmacokinetics of PLN-74809 in healthy volunteers.
Method: Immunohistochemistry (IHC) and enzyme-linked immunosorbent (ELISA)-based assays were used to evaluate expression of $\alpha_V\beta_6$ and $\alpha_V\beta_1$ in human tissue samples from PSC and PBC patients. Anti-fibrotic properties of PLN-74809 or PLN-75068 were evaluated *in vivo* in two mouse models of biliary fibrosis (Mdr2$^{-/-}$ and DDC diet) and in precision-cut liver tissue slices (PCLivS) from PSC and PBC patient tissue explants by IHC, hydroxyproline quantitation, and/or gene expression analysis. Phase 1 studies were conducted in healthy volunteers to evaluate safety and pharmacokinetics of PLN-74809.
Results: Integrins $\alpha_V\beta_6$ and $\alpha_V\beta_1$ were significantly elevated in fibrotic Mdr2$^{-/-}$ mice and DDC-fed mice, and in PSC and PBC patient liver tissue. PLN-74809 and PLN-75068 reduced both relative hepatic collagen levels and serum alkaline phosphatase levels in Mdr2$^{-/-}$ mice and DDC-fed mice, respectively. PLN-74809 reduced hepatic TGF-β signaling in Mdr2$^{-/-}$ mice and PLN-75068 reduced myofibroblasts in DDC-fed mice. PLN-74809 significantly reduced collagen gene expression in PCLivS from PSC and PBC patient tissue explants. Phase 1 studies of PLN-74809 demonstrated good oral bioavailability and tolerability, with the half-life supportive of once-daily dosing.
Conclusion: Dual inhibition of $\alpha_V\beta_6$ and $\alpha_V\beta_1$ with PLN-74809 or PLN-75068 reduced fibrosis in preclinical models of biliary fibrosis and in PCLivS from PSC and PBC patient tissue explants. Phase 2 evaluation of PLN-74809 in idiopathic pulmonary fibrosis and PSC patients is being planned.

EASL | JOURNAL OF HEPATOLOGY

From liver transplantation to systemic therapy in Hepatocellular Carcinoma

AS145

The concept of time-varying therapeutic hierarchy for patients with hepatocellular carcinoma: a multicenter cohort study. On behalf of the ITA.LI.CA study group

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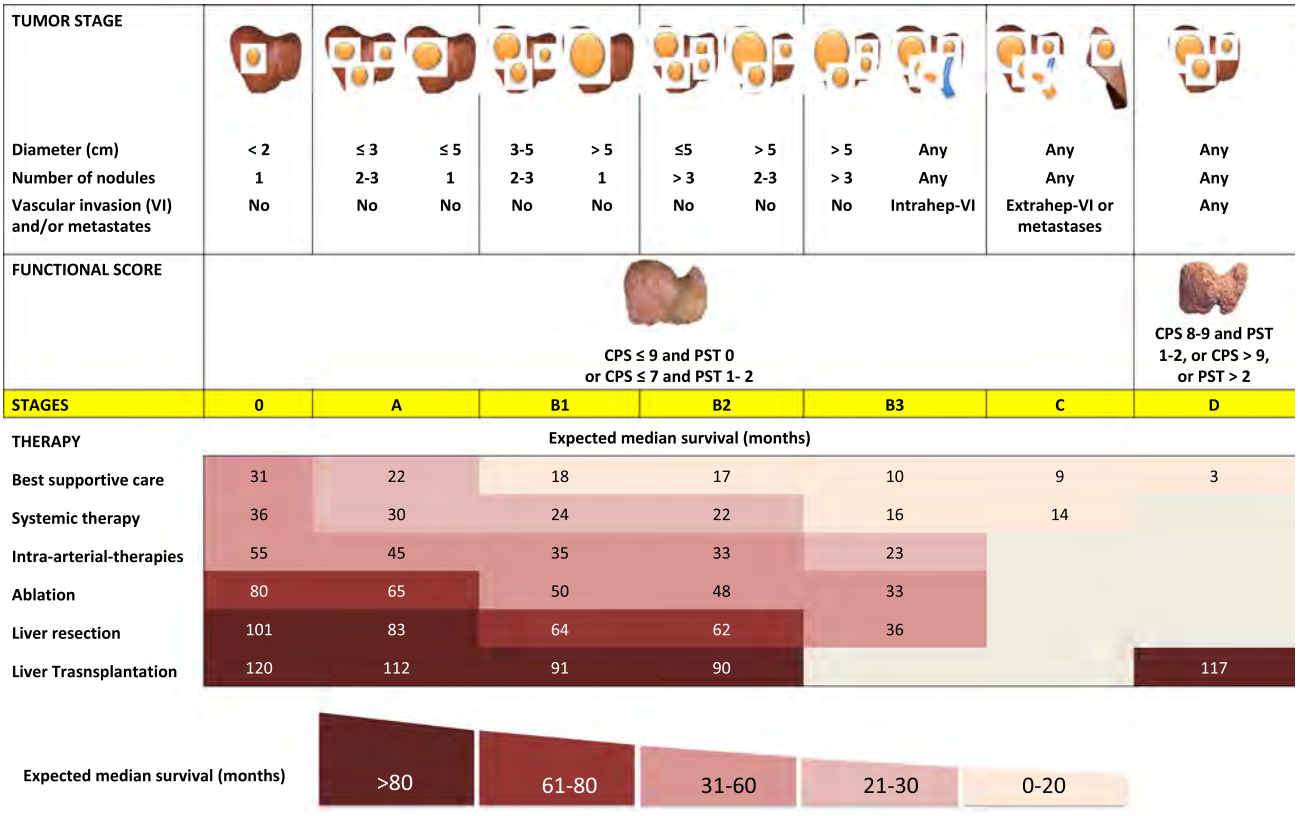
Background and Aims: While prognostic studies usually focus only on the first (or the main) treatment, the oncological history of patients with hepatocellular carcinoma (HCC) is characterized by a sequence of different treatment approaches. We sought to evaluate the survival benefit of sequential HCC therapies using a time varying multivariable survival model applied to a large cohort of HCC patients.

Method: We considered 6191 treatment strategies performed in 2800 HCC patients recorded in a prospectively collected multicenter Italian database from 2008 trough 2016.

We carried out a time-varying (TV) survival analysis where the total follow-up time for each patient was split into several observations accounting for each treatment procedure where appropriate. Before each treatment decision, patients were completely re-staged so that



Abbreviations. CPS, Child Pugh score; PST, performance status; VI, vascular invasion; Intrahep, intra-hepatic; Extrahep, extra-hepatic.

Figure 1: (abstract: AS145): The concept of "therapeutic hierarchy" is reported in association with the ITA.LI.CA simplified staging for treatment allocation derived from the last ITA.LI.CA study.
According to this approach, treatment choice is partially independent from the disease stage. In fact, for stages 0 to B2, all therapeutic solutions are available in a hierarchical order (from LT to BSC); for stage B3 only LT is contraindicated due to an unacceptable risk of HCC recurrence; for stage C, only systemic therapy and BSC are suggested; for stage D, LT and BSC are the only possible therapies.

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all re-assessed variables (i.e. liver function, tumor characteristics, therapy) were studied as TV parameters. A TV multivariable survival model was then used to evaluate the survival benefit of each treatment strategy (liver transplantation = LT, liver resection = RES, ablation = ABL, intra-arterial therapy = IAT, Sorafenib = SOR) over best supportive care (BSC). The survival benefit of HCC treatment was described as hazard ratio (HR), 95% confidence interval (CI), using BSC as reference value.

Results: The 6191 treatment strategies were: LT = 155, RES = 589; ABL 1728; IAT = 2184; SOR = 708; BSC = 827.

In the TV multivariable survival model, treatment strategy showed an independent effect on survival. The TV survival benefit of different therapies over BSC was: LT = 0.29 (0.24–0.36); RES = 0.30 (0.25–0.36); ABL 0.38 (0.33–0.43); IAT = 0.51 (0.45–0.57); SOR = 0.78 (0.67–0.90). Other significant variables in the multivariable survival model resulted: female gender, lnAFP (TV variable), and Italian Liver Cancer (ITA.LI.CA) stage (TV variable).

Conclusion: We demonstrated a decreasing TV survival benefit from surgical to systemic therapies in a large Italian cohort of HCC patients. This TV therapeutic hierarchy was independent from patient, liver function, and tumor characteristics.

AS146

A novel tailored prognosis calculator for the individualized curative treatments allocation of HCC patients within the Mmilan criteria

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Background and Aims: Controversies always exist during multidisciplinary treatment (MDT) decision making for hepatocellular carcinoma (HCC) within the Milan criteria (MC) due to the lack of evidence-based studies of composite multi-parametric evaluations among three potential curative therapies: liver transplantation (LT), liver resection (LR) and local ablation (LA). However, the prognosis prediction algorithm for HCC within the MC has never been explored. We aimed to develop a prognosis calculator for the individualized curative treatments allocation and assist with MDT decision making for these patients.

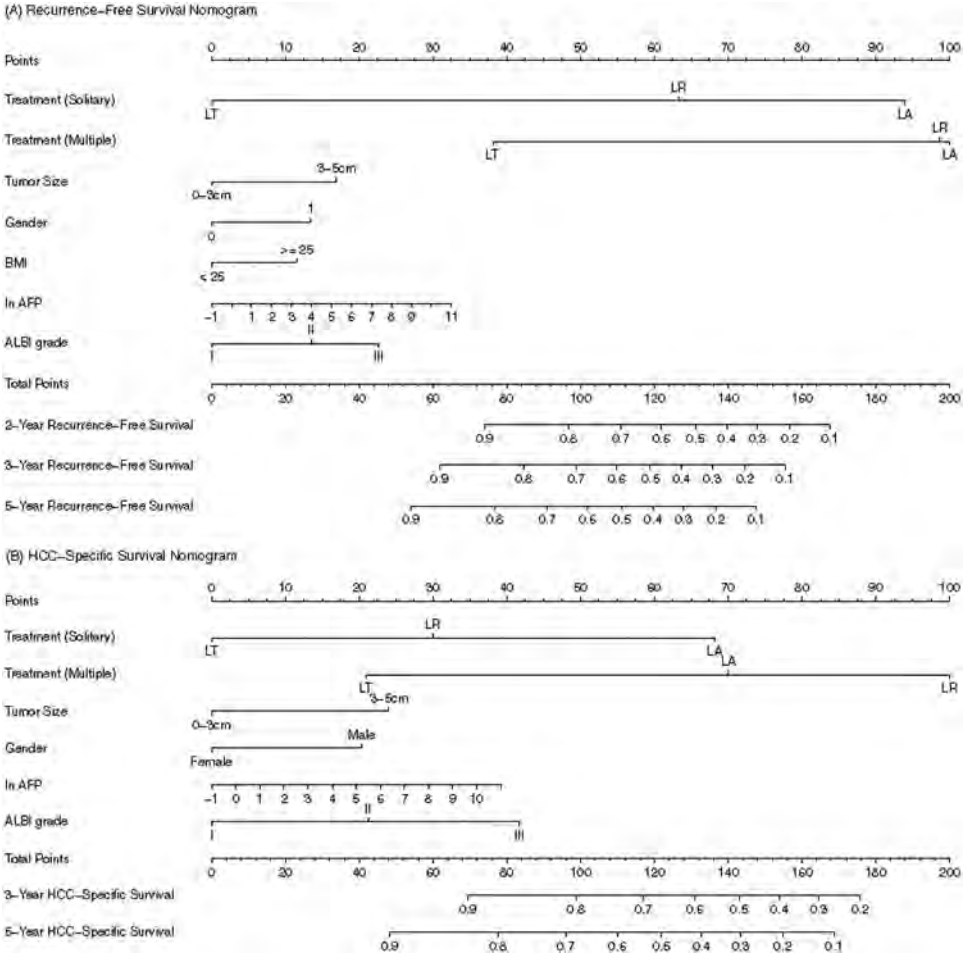

Figure: (abstract: AS146)

Method: Between July 2009 and May 2016, a total of 746 consecutive HCC patients within the MC underwent LT, LR and LA were enrolled and randomly divided into training (n = 501) and validation (n = 245) cohorts. Recurrence free survival (RFS), HCC-specific survival (HSS) and overall survival (OS) among the three treatment groups and subgroups were compared after inverse probability of treatment weighting (IPTW) to overcome treatment selection bias. Prediction models of RFS and HSS were developed and nomograms for RFS and HSS were derived and validated with the calibration, discrimination and risk stratifications.
Results: The median follow-up was 56.9 months. LT showed the best outcomes (LT vs. LR vs. LA: 86.8% vs. 50.7% vs. 26.0% for 5-year RFS and 85.2% vs. 72.6% vs. 47.1% for 5-year OS), and LA showed the highest proportion of recurrence within the MC. RFS and OS of LR and LA were similar in subgroup multiple tumours with 0–3 cm, but LA showed higher proportion of recurrence within the MC. Nomograms of RFS and HSS based on gender, body mass index (BMI), treatment allocation, tumour number (solitary or multiple), tumour size (3–5 cm vs. ≤3 cm), alpha-fetoprotein (AFP) and albumin-bilirubin (ALBI) grading were constructed and showed satisfactory performance in the validation cohort. The two models were validated with satisfactory discrimination abilities (c indexes for RFS: 0.80, 0.82, and 0.87 at 2, 3, and 5 years and c index for HSS: 0.79 and 0.86 at 3 and 5 years), calibration curves and risk stratifications of RFS and HSS. The online prognosis calculator for curative treatments allocation of HCC patients within the MC according to the two models was successfully established, please see the website: https://yingwu.shinyapps.io/Tianjin-PC-MDT/.
Conclusion: The prognosis calculator for HCC within the MC showed feasibility on individualized curative treatment allocation to assist with MDT decision making.

AS147

Refinining the post transplant outcomes prediction of Metroticket 2.0 through mRECIST criteria

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Background and Aims: The combination of morphology and biology represents the most useful approach to select candidates with hepatocellular carcinoma (HCC) for liver transplantation (LT) at acceptable risk of recurrence. However, the weight of response to neo-adjuvant therapies remains partially unsolved for most of post-LT prediction models. Aim of this study was to embed radiological response in the Metroticket 2.0 model for post-LT prediction of "*HCC-related death*" to provide more usefulness in the modern clinical scenario.
Method: Data from 988 transplanted patients (2000–2015) with adequate clinical and radiological information were included. The last radiological assessment before LT was reviewed according to the mRECIST criteria. Competing-risk analysis was applied. The added value of including radiological response into the Metroticket 2.0 was explored through the category-based Net Reclassification Improvement (NRI).
Results: At last radiological assessment prior to LT, complete response (CR) was diagnosed in 35.9%, partial response/stable disease (PR/SD) in 29.7% and progressive disease (PD) in 34.4%. Patients with CR had 5-year rates of "*HCC-related death*" of 2.9%, those with PR/SD had 8.0% and those with PD had 12.8% ($P < 0.001$). Log_{10}AFP ($p < 0.001$) and the sum of number and diameter of the tumour/s ($p = 0.001$) were determinants of "*HCC-related death*" for PR/SD and PD patients, with different hazards. To maintain the post-LT 5-year incidence of "*HCC-related death*" <30%, the Metroticket 2.0 criteria were restricted in presence of PD, correctly reclassifying 16.7% of patients who died from "*HCC-related death,*" at the expenditure of 7.0% of patients who did not have the event. The overall NRI was of 9.7.

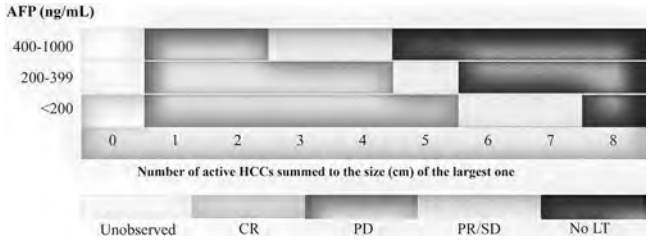

Figure 1: Identification of transplantable tumour on the basis of HCC morphology parameters (largest vital tumor size + number of vital tumor nodules) and biology (AFP and last radiological mRECIST assessment), determined at pre-LT radiology The darkest areas describe a 5-year "HCC-related death" above the safety threshold of 30%.

Conclusion: Inclusion of mRECIST criteria within the Metroticket 2.0 framework can provide further clinical information when judging eligibility for candidates to LT.

AS148

Clinical-radiomics analysis for preoperative prediction of objective response to transarterial chemoembolization in hepatocellular carcinoma

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Background and Aims: Preoperative decision-making for selecting patients who have an objective response to transarterial chemoembolization (TACE) remains challenging. Therefore, we aimed to develop and validate a clinical-radiomic model (CR-model) for preoperatively predicting the treatment response to TACE in intermediate-stage hepatocellular carcinoma (HCC) patients.
Method: A total of 595 patients with intermediate-stage HCC were retrospectively included. Treatment response-related radiomic signature (TRR-signature) was built on 3,404 radiomic features from 4 target volumes. The TRR-signature and 22 clinical factors were integrated into a predictive model, the CR-model, with multivariate logistic regression. The performance of this model was evaluated by the calibration curves and the area under the receiver operating characteristic curves (AUCs).
Results: Five independent predictors, including a TRR-signature-1 ($P < 0.001$) and 4 clinical factors, including AFP ($P = 0.004$), Barcelona Clinic Liver Cancer System (BCLC) stage B subclassification ($P = 0.01$), tumor location ($P = 0.039$), and arterial hyperenhancement ($P = 0.050$), were taken into the CR-model. The calibration curves for the probability of objective response showed optimal agreement between nomogram prediction and actual observation. The AUCs of this model in training, and the internal and external validation cohorts were 0.96, 0.94, and 0.90, respectively. As a prognostic factor,

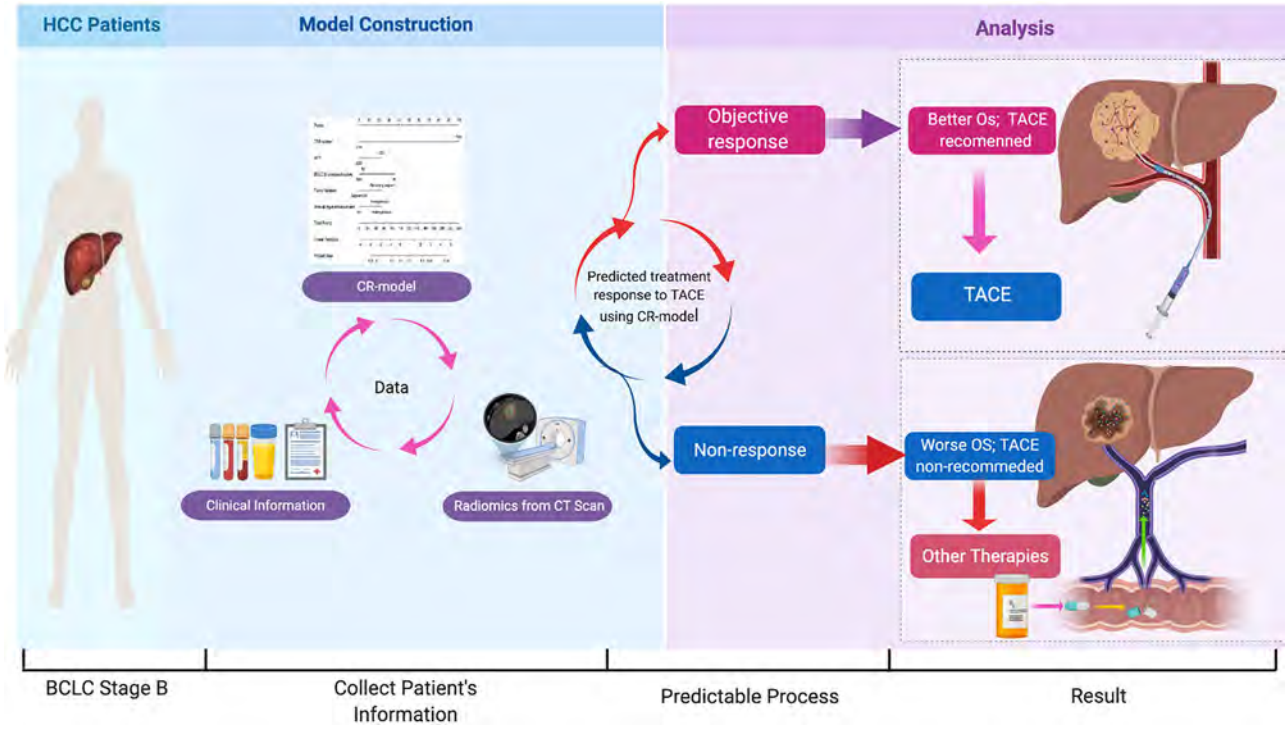

Figure: (abstract: AS148)

the treatment response (objective vs non-response) predicted by the CR-model showed significant differences of overall survival in the external validation cohort (HR, 2.41; 95%CI, 1.59 to 3.66; $P < 0.001$). Notably, it also allowed significant distinction between survival curves within each BCLC B subclassification.

Conclusion: The clinical-radiomic model demonstrates a good performance for predicting treatment response, and provides a powerful tool to assist the clinicians in patient selection.

AS149

Optimal time-point of response assessment for predicting survival is associated with tumor burden in hepatocellular carcinoma receiving repeated transarterial chemoembolization

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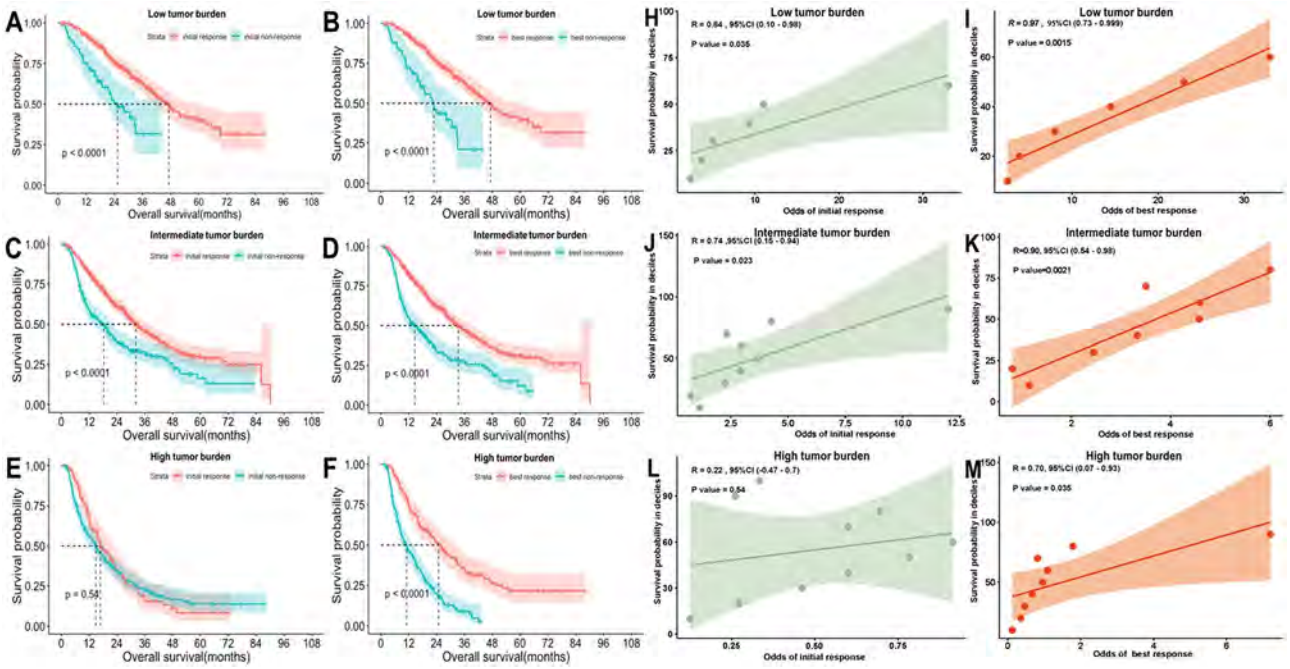
Background and Aims: It's unknown that whether initial response or best response is used to predict overall survival (OS) in hepatocellular carcinoma (HCC) receiving repeated transarterial chemoembolization (TACE). We sought to investigate their prognostic value and practicality as potential surrogate of OS.

Method: We conducted a retrospective study of treatment-naïve patients with unresectable HCC, well-preserved liver function, and a performance status score of 0–1 undergoing TACE between 1/2010 and 5/2016. Time-dependent Cox regression analysis and Pearson's correlation coefficient were used to determine the predictor and surrogacy.

Results: We identified 1549 eligible patients from 17 academic hospitals and stratified them into strata of low, intermediate and high tumor burden, based on our previously proposed "Six-and-twelve" score. Significant interaction between tumor burden and initial as well as best response were observed (both $p_{interaction} < 0.001$). In stratification analyses, initial and best responses could effectively predict and strongly correlated with OS in low (adjusted hazard ratio (HR): 2.55 and 2.95, respectively, both $p < 0.001$; $r = 0.84$, $p = 0.035$



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and r = 0.97, p = 0.002, respectively) and intermediate strata (adjusted HR: 1.81 and 2.22, respectively, both p < 0.001; r = 0.74, p = 0.023, and r = 0.9, r = 0.002, respectively), with high concordance in these groups (kappa value: 0.92 and 0.88, respectively). Conversely, only best response but not initial response served to be predictable (adjusted HR: 2.61, p < 0.001, and adjusted HR: 1.08, p = 0.537, respectively) and significantly associated with OS (r = 0.70, p = 0.035, and r = 0.22, r = 0.54, respectively) in high strata.

Conclusion: Initial response conferred assessing efficacy at early time, making it preferred and pragmatic surrogate of OS among low and intermediate strata, however, it was impracticable to high strata, where best response provided modest correlation with OS. These findings have implications for prognosis, stratification and trial design.

AS150

Regorafenib improves survival after sorafenib treatment in patients with recurrent hepatocellular carcinoma after liver transplantation, compared to best supportive care

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Background and Aims: Regorafenib (REGO) has been shown to be a safe second-line treatment for hepatocellular carcinoma (HCC) recurrence after liver transplantation (LT). The aim of this study was to compare the overall survival (OS) of REGO to best supportive care (BSC) after sorafenib (SOR)-discontinuation in LT patients.

Method: We conducted a retrospective, multicentre, international study, including all patients with HCC recurrence after LT who discontinued SOR. The REGO-group included patients treated with REGO after SOR-discontinuation, due to progression in tolerant patients, the control-group included all patients treated with BSC due to REGO unavailability, symptomatic progression or SOR-intolerance. The primary end-point was OS from SOR-discontinuation.

Results: Included were 96 LT-patients: 32 treated with REGO after HCC progression under SOR (group-A) and 64 patients receiving BSC after SOR-discontinuation 31 SOR-tolerant in progression (group-B), 20 SOR-intolerant and 13 discontinued SOR for other

reason (symptomatic progression, non-liver complications, patient's decision). The median survival for the whole cohort since SOR-start was 19.3 (13.4–25.1) months (mos). The comparative analyses were conducted between group-A and group-B, with similar clinical and demographic features [i.e. mTORi treatment 63% vs 81% (0.11); SOR 800 mg 41% vs 23% (p = 0.12); SOR treatment duration 11.1 (0.7–76.7) vs 7.8 (0.9–96.3) mos (p = 0.65); at SOR-discontinuation: ECOG-PS 0–1 100% vs 90% (p = 0.29); tumor burden: liver only 6% vs 10%, extra-hepatic only 44% vs 45%, both 50% vs 45% (p = 85); AFP: 134 (1–209,630) vs 1044 (1–88,950) ng/ml (p = 0.83)]. All the 32 patients treated with REGO [treatment duration 7.0 (5.5–8.4) mos] had at least 1 adverse event (grade 3/4: fatigue in 8 and dermatological reaction in 5). Median follow-up since SOR-discontinuation was 12.3 (0.6–42.2) mos for group-A and 4.5 (0.0–22.3) for group-B (p = 0.0006). At data-lock, 66% patients had died in group-A and 94% in group-B, symptomatic tumor progression being the main cause of death. The median OS from SOR-discontinuation was 14 mos (95%CI:10–18) for group-A and 4.5 mos (95%CI:24–66) for group-B (p < 0.005). The overall OS from SOR-start was 32.6 mos (95%CI:18–46) for the SOR-REGO group compared to 14.3 mos (95%CI:7–21) for the SOR-BSC sequence in the group-B (p = 0.001).

Conclusion: REGO is a safe and effective second line option after SOR-progression in patients with HCC recurrence after LT.

HCV Long-term management

AS151

The dynamics of FIB4 after sustained viral response predicts the risk of liver-related complication in HCV cirrhosis (ANRS CO12 Cirvir)

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Background and Aims: Sustained viral response (SVR) significantly improves the prognosis in patients with cirrhosis due to hepatitis C virus (HCV), but does not totally eliminate further occurrence of liver-related complications (LRC). We aimed to evaluate whether the evolution of blood tests after SVR correlates with the residual risk of LRC and allows stratification of the prognosis in HCV cirrhotic patients.
Method: 695 patients with biopsy-proven HCV cirrhosis prospectively recruited in 35 French centres (ANRS CO12 CirVir cohort) who experienced SVR were included in the analysis. Data (clinics and biology) were collected at SVR (study baseline) and during the follow-up. The primary outcome was the first occurrence of LRC, a composite endpoint including cirrhosis complication (ascites, variceal bleeding, encephalopathy) and/or hepatocellular carcinoma (HCC). Time-dependent ROC curves were used to identify the best prognostic biomarker. Joint models accounting for the biomarker trajectory and LRC occurrence were developed to compute dynamic predictions. The predictive accuracy of these dynamic predictions was assessed using approximate cross-validated estimator (CVPOL) of expected prognostic observed cross-entropy. A web Shiny application was finally developed for clinical practice.
Results: A first LRC occurred in 50 patients (25 cirrhosis complications, 25 HCCs) during the median 3.7 [1.6–7.4] years follow-up following SVR. FIB4 provided the highest time-dependent ROC curve compared to the other biomarkers tested (APRI, AST, ALT, GGT, platelets), with values fluctuating around 0.8 at all horizons. Joint models identified four patient profiles using diabetes, baseline FIB4 and FIB4 evolution during the follow-up. CVPOL computed for a time at prediction from 1 to 5 years after SVR showed good predictive accuracy with results ranging from 0.08 to 0.46. Goodness of fit was assessed using predicted survival curves and observed weighted Kaplan Meier curves showed (Figure A). The web Shiny application developed for clinicians depicts the predicted risk of LRC after SVR based on the evolution of FIB4 results and diabetes status (Figure B).
Conclusion: The evolution of simple parameters (FIB4 and diabetes status) predicts the residual risk of liver-related complication after sustained viral response in patients with HCV cirrhosis. Such assessment could help to refine the patient management, especially for the most at-risk patients.

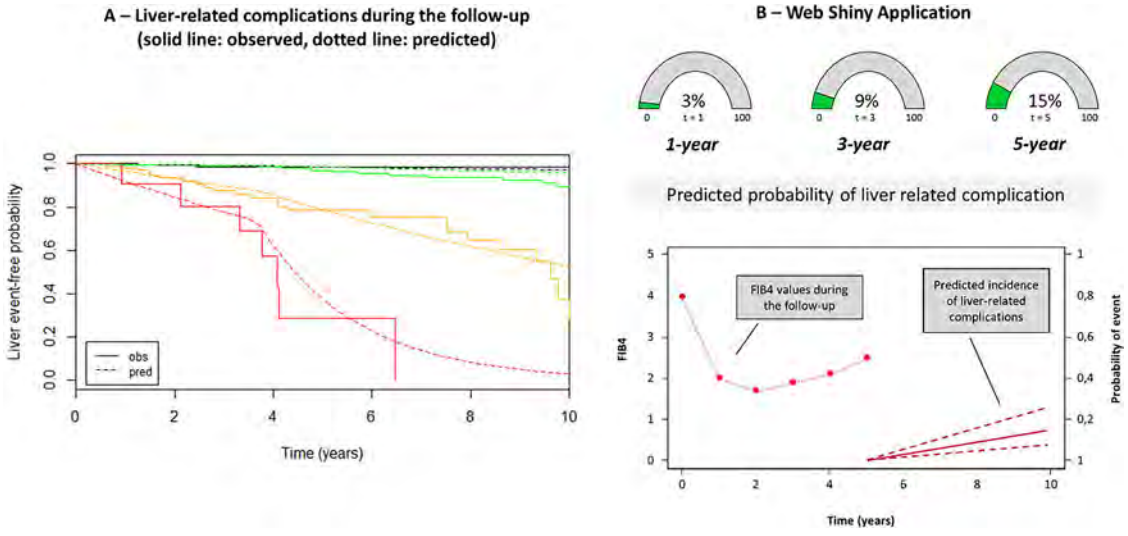

Figure: (abstract: AS151)

AS152

Non-invasive monitoring of liver disease regression in patients with advanced chronic liver disease after sustained virologic response to INF-free therapies

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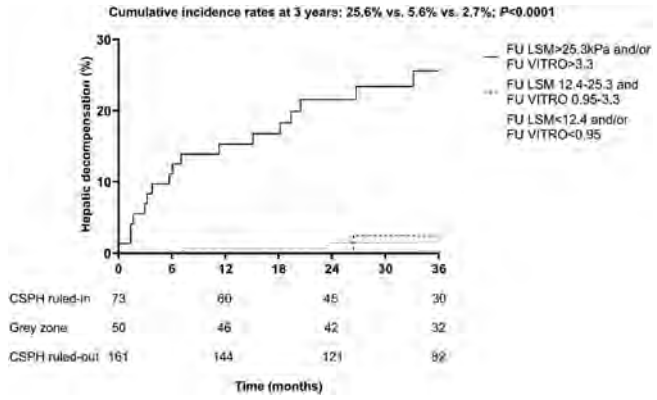
Background and Aims: Hepatic venous pressure gradient (HVPG) predicts hepatic decompensation in patients with advanced chronic liver disease (ACLD) who achieved sustained virologic response (SVR) to interferon (IFN)-free therapies. However, non-invasive alternatives are needed for risk stratification after HCV cure.
Thus, we investigated the predictive value of non-invasive surrogates of portal hypertension (liver stiffness measurement [LSM] by transient elastography [TE] and VWF/platelet count ratio [VITRO]) for post-treatment hepatic decompensation in patients with pre-treatment ACLD who achieved SVR.
Method: Two hundred and eighty-four patients with information on paired pre- and post-treatment (follow-up [FU]) LSM and VITRO were followed after the end of antiviral therapy.
Results: Prior to IFN-free therapy, 258 (90.8%) patients had compensated, while 26 had (9.2%) decompensated ACLD. The mean pre-treatment MELD score was 8.6 ± 2.5points and the median LSM and VITRO values were of 17.1 (15.2)kPa and 1.66 (1.97), respectively. FU LSM (area under the curve [AUC]: 0.836 [95%CI: 0.745–0.907]) and FU VITRO score (0.853 [95%CI:0.778–0.928]) showed the best performance for predicting hepatic decompensation during FU. Both variables were independently predictive of hepatic decompensation in a Cox regression model (adjusted hazard ratio 1.031 [95%CI: 1.009–1.055] per LSM-kPa and 1.184 [95%CI: 1.033–1.358] per VITRO-point), even after adjusting for previous hepatic decompensation as well as post-treatment MELD and albumin levels.
A previously proposed combined approach (FU LSM<12.4 kPa and/or FU VITRO <0.95) was able to rule-out clinically significant portal hypertension (CSPH, HVPG ≥ 10 mmHg) at FU in the majority (56.3%) of patients – who had a negligible risk of hepatic decompensation after the end of antiviral therapy (2.7% at 3 years; Figure). In contrast, in patients in whom FU CSPH was ruled-in by non-invasive diagnostics (26% of the study population; FU LSM>25.3 kPa and/or FU VITRO >3.3), the risk of hepatic decompensation within 3 years post-treatment was high (25.6%). Patients within the diagnostic grey zone for FU CSPH (17.6% of the study population) had a numerically increased, but still a very low risk of hepatic decompensation during FU (5.6%).



Conclusion: FU LSM and FU VITRO score are strongly and independently predictive of post-treatment hepatic decompensation in ACLD patients who have achieved SVR to IFN-free therapies. An algorithm combining these non-invasive markers of portal hypertension that was developed to rule-in or rule-out FU CSPH identified populations at negligible versus high risk for hepatic decompensation. Accordingly, this algorithm enables risk stratification after SVR, and thus, facilitates personalized FU.

AS153

HIV co-infection and risk of morbidity and mortality in HCV patients treated by DAA

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Background and Aims: HIV co-infection leads to increased mortality, liver disease progression and extra-hepatic manifestations in HCV-infected patients. DAA lead to high SVR rates and decrease the risk of disease progression. We compared risks of liver-related events, liver-related mortality and non-liver-related mortality in HIV/HCV co-infected and HCV mono-infected patients treated by DAA.
Method: Four HCV mono-infected participants from the ANRS CO22 HEPATHER cohort were matched on age and sex to each HIV/HCV co-infected participant from the ANRS CO13 HEPAVIH cohort. All participants were treated by DAA between March 2014 and December 2017. Cox proportional Hazards models adjusted on age, sex, duration since HCV diagnosis, HCV contamination routes, HCV genotype, cirrhosis status, tobacco and alcohol consumption were used.
Results: 592 HIV/HCV co-infected and 2049 HCV mono-infected were included. Median age was 52.9 years [IQR: 49.6; 56.7] and 53.3 years [IQR: 49.6; 56.9]; 436 (73.6%) and 1498 (73.1%) were men; median duration since HCV diagnosis was 18.0 years [IQR: 12.4; 22.2] and 14.5 years [6.4; 20.8], and 159 (28.8%) and 793 (41.2%) were cirrhotic, respectively. Participants were predominantly treated by Sofosbuvir and Ledipasvir (48.8% and 34.5%, respectively) or Sofosbuvir and Daclatasvir (32.6% and 31.2%, respectively) and SVR was observed in 92.9% and 94.6% overall, respectively. After a median follow-up of 2.8 years, incidence of liver-related events was 12.4 per 1000 PY (95%CI: 7.7; 19.9) in HIV/HCV co-infected and 13.4 per 1000PY (95%CI: 10.5; 17.0) in HCV mono-infected ($p = 0.78$). Incidence of liver-related mortality was 5.6 per 1000 PY (95%CI: 2.8; 11.1) in HIV/HCV co-infected and 4.9 per 1000 PY (95%CI: 3.4; 7.1) in HCV mono-infected ($p = 0.76$). Incidence of non-liver-related mortality was 12.5 per 1000 PY (95%CI: 7.9; 19.8) in HIV/HCV co-infected and 4.9 per 1000 PY (95%CI: 3.4; 7.1) in HCV mono-infected ($p < 0.01$). After adjustment, HIV co-infection was not associated with a higher risk of liver-related events (HR = 0.67 95%CI: 0.27; 1.67) or liver-related-mortality (HR = 0.94 95%CI: 0.19; 4.67), but the risk of non-liver-related mortality (HR = 2.67 95%CI: 0.97; 7.37) tended to be higher in HIV/HCV co-infected.
Conclusion: After DAA treatment, the risk of liver-related events and liver-related mortality were similar between HIV/HCV co-infected and HCV mono-infected but HIV co-infection tended to increase the risk of non-liver-related mortality.

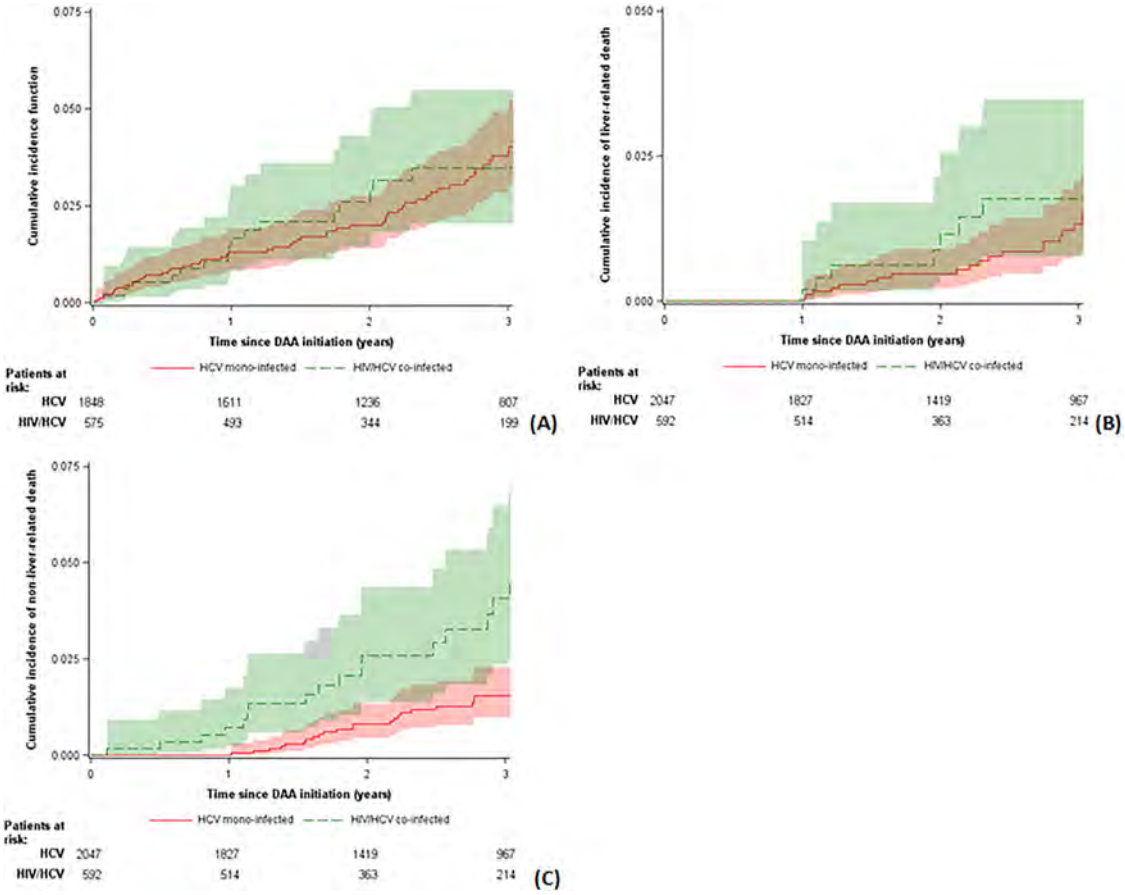

Figure 1: (abstract: AS153): Cumulative incidences (and 95% confidence intervals) of liver-related-events (A), liver-related death (B) and non-liver-related death (C), in HIV/HCV co-infected (in green) and HCV mono-infected (in red) from the ANRS CO13 HEPAVIH.

AS154

Predictive models for hepatocellular carcinoma (HCC) occurrence in patients with chronic hepatitis C and sustained virological response (SVR) achieved with direct acting anti-viral (DAA) included in the ANRS CO22 hepather cohort

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Background and Aims: Despite viral eradication, patients with chronic hepatitis C have a residual risk of HCC especially in cases of pre-therapeutic advanced liver fibrosis. HCC risk factors and scores, well established before viral eradication, remain to be determined after SVR. For this purpose, we analyzed HCC predictive factors after SVR12 and developed a predictive score whose performance was compared to previous published scores.
Method: Among 12,324 HBsAg-negative patients with HCV chronic hepatitis enrolled in ANRS CO22 HEPATHER cohort, we selected those non-liver transplants, HCC-free and without missing values of interest who achieved SVR 12 weeks after DAA treatment. HCC predictive models were developed by Cox multivariate and validated in all included patients then specifically in those with cirrhosis. Calibration, discrimination and predicted risk classification of HCC were assessed and compared to the new published scores estimates. The primary endpoint was the area under the integrated time-dependent ROC curve (i-AUC).
Results: During follow-up (median 2.23 years –IQR 1.16–3.28; maximum 6.12), 220 (194 with cirrhosis) out of 7,752 selected patients developed an HCC. Eight independent variables were associated with HCC occurrence: male gender (HR 1.79 CI95%: 1.27–2.53), age at SVR >64 years (HR 2.45 CI95%: 1.46–4.12), advanced liver fibrosis (F3: HR 5.27, CI95%: 1.91–14.57; F4: HR 9.86, CI95%: 3.94–24.69), genotype 3 (HR 1.79 CI95%: 1.23–2.60), esophageal varices (HR 2.79, CI95%: 2.01–3.87, baseline serum AFP >5.5 ng/Ml (HR 1.36, CI95%: 1.02–1.80), ASAT to Platelets Ratio Index (APRI) >2 at end of treatment (HR 1.91, CI95%: 1.29–2.82) and past interferon-based regimen(s) with or without ribavirin (HR 1.71, CI95%: 1.20–2.44). An HCC risk score was established using these variables allowing the stratification of patients into three groups of risk level: high (n = 144, score ≥ 19/28), intermediate (n = 1677) and low (n = 5931, score < 11 /28) with 1 and 3-yrs HCC incidences of 7.08 and 18.00%, 3.00 and 8.34% and 0.37 and 1.13%, respectively. The performance of this score was higher than the published re-estimated scores in all selected patients with an i-AUC of 0.78 vs. 0.53–0.72. The models were well calibrated. Among patients with cirrhosis (n = 2836), beside liver fibrosis, all the 7 independent predictors were selected to establish a risk score of 14 points with iAUC of 0.71 vs 0.49–0.67.
Conclusion: The HEPATHER cohort HCC score has good short-term predictive performance in HCV- patients who achieved SVR12 after DAA treatment allowing to identify low-risk patients (HCC 3 years-incidence <1.5%, n = 5931 i.e 76.5%) in whom HCC screening may be superfluous in the first 3 years after SVR.

AS155

A simple score for HCC risk stratification in CHC patients with cirrhosis or advanced hepatic fibrosis who achieved SVR following DAA therapy

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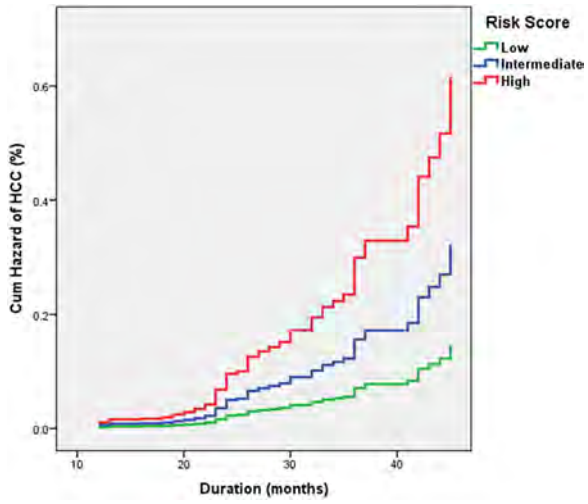
Background and Aims: Patients with advanced fibrosis or cirrhosis before achieving a sustained virologic response (SVR) to direct-acting antiviral (DAA) treatment for hepatitis C virus (HCV) infection continue to have a risk for hepatocellular carcinoma (HCC) for several years. However, the heterogeneity and substantial intra-individual variation in this risk have encouraged the development of scoring system that predict risk of HCC occurrence. The aim of this work was to develop a model that offer individualized patient HCC risk prediction.

Method: This is a prospective study including chronic hepatitis C (CHC) patients with liver cirrhosis (F4) or advanced hepatic fibrosis (F3) who achieved SVR following DAAs from January 2015 until August 2017, conducted at the Egyptian Liver Research Institute and Hospital (ELRIAH). Clinically relevant baseline parameters were collected and patients were followed up every 6 months for up to 45 months. Factors associated with HCC were identified through multivariable Cox regression and used to develop a scoring model for prediction of HCC risk and the performance of the model was assessed by area under the Receiver operating characteristic (ROC) curve.



Results: 2326 CHC consecutive patients (1734 with F4 stage and 638 patients with F3) who achieved SVR were included. Follow up period was 23.51 ± 8.21 months (range 12–45 months). 109 patients (4.7%) developed HCC during the follow up period, out of them 101 patients had cirrhosis before initiation of DAA therapy and the remaining 8 patients had F3 liver fibrosis. Using multivariable Cox regression age, sex, serum albumin, α feto-protein (AFP) and pre-treatment fibrosis stage were identified as risk factors for HCC. To improve clinical utility, a simple predictive model (GS score) was constructed by assigning points for each covariate in proportion to the hazard ratios in the final multivariable model: age (≤54 vs. >54 years), sex (male vs. female), serum albumin (<3.8 vs. ≥ 3.8 g/dL), AFP (≤20 vs. >20 ng/ml) and pre-treatment fibrosis stage (F3 vs. F4). Using ROC analysis, patients were then stratified into three groups (low, medium and high risk) based on the score (AUROC = 0.824). The proposed model showed high predictive accuracy and the 2 year cumulative HCC incidence using Kaplan-Meier method was 2%, 4.5% and 10.3% in the low-risk, medium-risk and high-risk groups respectively.

Conclusion: GS score, using readily available parameters, has good predictive ability for occurrence of HCC after eradication of HCV. If validated, it may help to individualize HCC screening among CHC patients with liver cirrhosis and advanced hepatic fibrosis.

AS156

Virological characterization of patients with chronic hepatitis C and failure to a glecaprevir/pibrentasvir or voxilaprevir/velpatasvir/sofosbuvir treatment in the international shared collaboration

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Background and Aims: Treatment of chronic hepatitis C virus (HCV) infection with new regimens [Glecaprevir and Pibrentasvir (G/P) or Voxilaprevir/Velpatasvir/Sofosbuvir (VVS) results in high sustained virologic response (SVR) rates both in clinical trials and real world. Here we present real world data on the characteristics of G/P or VSS failure patients from the real world international SHARED collaboration.

Method: Virological and clinical Information were obtained from resistance databases within the SHARED collaboration. Population sequencing of NS3, NS5A and NSB5 was conducted and RASs conferring a >2-fold increased DAA susceptibility were analyzed. Clinical and virological data were collected retrospectively.
Results: Altogether 133 patients had a virologic treatment failure to G/P or VVS; 77% of patients were male, with a mean age of 56 years (IQR, 49–63). The majority of patients was infected with genotype (GT) 3a (n = 50, 38%), while 37 individuals had GT1a, 17 had GT1b, 17 had GT2c, 4 had GT2a, 5 had GT4d and 3 was infected with rare subtypes (GT3b, GT4k and GT6q). Cirrhosis was detected in 34 patients. Ninety-nine patients had a virologic failure to G/P: 33% failed without any NS3 or NS5A RAS, while 57% of patients developed RASs in NS5A and 14% in NS3. NS5A RAS presence was different according to HCV GT (>70% in GT1a and GT3, 40% in GT1b and 21% in GT2a/c). The most frequent RASs were Y93H in NS5A and D/Q168L in NS3. Interestingly, a combination of two or more RASs in NS5A was frequently detected in GT1a and GT3 (two n = 36; three n = 8). Thirty-four patients had a virologic failure to VVS retreatment (mainly with GT3, GT1a and GT1b). Prior to VVS initiation, 76% of patients harbored NS5A RASs with high frequencies (60%) of Y93 variants, whereas NS3 D168 RASs were uncommon (30%). After VVS failure, the NS5A resistance profile was identical compared to baseline in the majority of patients (65%) and NS3 D168 frequencies were reduced (16%). NS5B SOF RASs were uncommon.
Conclusion: After G/P failure, NS5A RASs were frequently observed as dual and triple combination patterns, especially in patients infected by genotypes 3 and 1a. Failure to VVS was mainly observed in patients infected with genotype 3a, with rare occurrence of NS3 and NS5B RASs and a resistance profile of RASs in NS5A that was maintained from previous treatments.

NAFLD - Clinical except therapy

AS157

Liver disease progression and clinical outcomes in hepatic outcomes and survival fatty liver registry (HOTSURFR) study

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Background and Aims: In patients (pts) with NAFLD long-term liver outcomes and overall survival are incompletely characterized, particularly relative to the clinical phenotype and histological features.
Method: The HOTSURFR study, an international collaboration of 8 centers (France, Sweden, Germany, UK, Australia and Italy), included consecutive pts biopsied for suspected NAFLD between 2004 and 2011. Liver biopsy was read by a central pathologist and data on survival, liver-related events and cirrhosis occurrence were collected. Here we report the analysis of the first 473 pts (233 with centrally read biopsies) focusing on type 2 diabetes (T2D) status at baseline and follow-up and fibrosis stage according to the new EPoS 7-tier classification (no/mild fibrosis, stages 0–2; moderate advanced fibrosis, stages 3–4; cirrhosis stages 5–6).
Results: At baseline 66% of pts were men, median age was 53 years, 42% with BMI ≥ 30 kg/m^2, EPoS-F stage prevalence: 0–2, 73%; 3–4, 13%; 5–6, 14%. Median follow-up after biopsy was 9.5 yrs. 181 pts (38%) had T2D at baseline (Group A), 58 (12%) developed T2D (Group B) and 234 (49%) remained free of T2D (Group C). Death occurred in 48 pts, liver-related death in 16 pts, 52 pts developed cirrhosis and 48 pts liver-related events.
Overall 10 yr survival, liver-related death, and liver-related events were similar in Groups A/B and different from Group C (83%/87% vs 98%, p = 0.005; 7.6% /5.5% vs 0.9%, P = <0.001; 19%/11% vs 3.5%, p = 0.001, respectively). Annual incidence rate of liver-related events was 0.25% in EPoS-F0-1; 0.86% in EPoS-F2; 2.15% in EPoS-F3-4 and 6.66% in EPoS-F5-6. Baseline T2D and moderate fibrosis (EPoS-F3-4) independently predicted cirrhosis occurrence (HR 2.37 and HR 5.92, respectively). T2D and EPoS-F3-6) independently predicted liver-related events (HR 2.53 and HR 8.33, respectively). Group B had similar HRs as group A in all analyses for these outcomes.
Conclusion: In this ongoing, multicentric, consecutive, tertiary care, biopsied NAFLD population, the incidence of liver-related events ranged from 0.25 to 6.66%/yr depending on baseline fibrosis stage. Baseline or incident T2D is a major predictor of liver morbi-mortality. The new EPoS-F staging system has prognostic value for liver-related death and events.

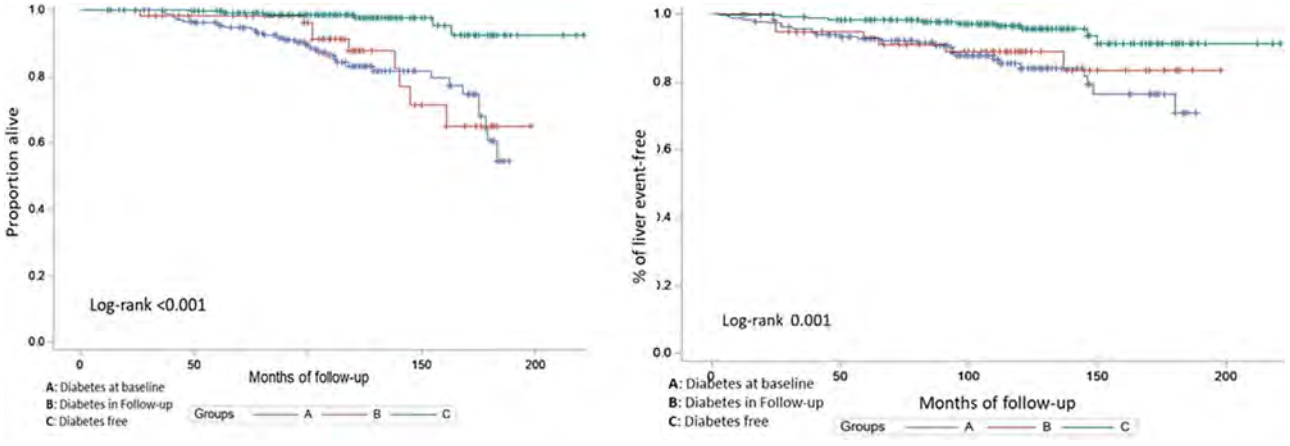

Figure: (abstract: AS157): Overall mortality stratified on diabetes status (left) and Incidence of liver complications stratified on diabetes status (Right).

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Causes of death in patients with non-alcoholic fatty liver disease (NAFLD): data from national vital statistics system (NVSS)

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Background and Aims: NAFLD is the most common cause of chronic liver disease (CLD) and among the top cause of liver-related mortality, cause of hepatocellular carcinoma and indication for liver transplantation. Since most of the data originates from tertiary care centers, comparable and consistent measures of cause of deaths among NAFLD at the population level have not been produced previously. Our aim is to quantify and describe all-cause deaths, liver-related and cancer deaths among NAFLD in the United States (U.S.) using a population-based mortality database.
Method: Mortality record from all death certificates filed in U.S. 2017 was utilized. Decedents with each CLD were classified by the International Classification of Diseases, 10th Revision (ICD-10) as an underlying or contributing cause of death. Cause-specific of deaths are based on the underlying cause of death. Liver-related deaths included liver cancer, cirrhosis and CLDs.
Results: For 2017, there were 2,776,829 decedent cases (20 years or older) in U.S. Of these, 83,154 (3.0%) were liver-related deaths (mean [SD] age, 64.6 [13.8] years) which ranked as the 8th leading cause of death. Alcoholic liver disease (ALD) was responsible for 27.9% of liver-related deaths; NAFLD, 26.3%; chronic hepatitis C (CHC) 12.1%; and chronic hepatitis B (CHB), 0.3%. Among decedents with NAFLD (n = 43,187), the four leading causes of death were liver-related (53.1%), cardiovascular disease (12.2%), non-liver cancer (6.6%) and diabetes-related (2.6%) deaths. The majority of cancer deaths among decedents with NAFLD came from solid cancers (79.6%). Although the leading cause of cancer death in decedents with NAFLD was liver cancer (42.6%), other solid cancers included lung cancer (8.5%), colorectal cancer (6.9%), pancreatic cancer (5.5%) and breast cancer (4.2%). Among decedents with NAFLD, causes of cancer death were different between males and females (Table).
Conclusion: NAFLD is the second leading cause of liver related mortality. Although liver cancer is the most common solid tumor in decedents with NAFLD, lung cancer, colorectal, pancreatic and breast cancer are also the other common causes of cancer-related deaths.

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A transcriptomic signature predicting fibrosis progression in a large European cohort of patients with histologically characterised NAFLD

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Table. Causes of Cancer Deaths in Decedents with NAFLD, Stratified by Sex, U.S. 2017

	NAFLD			P
	Both	Female	Male	
Solid Cancer	3919 (79.59%)	1273 (76.09%)	2646 (81.39%)	<.0001
Causes				
Liver and intrahepatic bile ducts	2095 (42.55%)	517 (30.90%)	1578 (48.54%)	<.0001
Trachea, bronchus and lung	420 (8.53%)	142 (8.49%)	278 (8.55%)	0.9398
Colon, rectum and anus	339 (6.88%)	121 (7.23%)	218 (6.71%)	0.4892
Pancreas	273 (5.54%)	117 (6.99%)	156 (4.80%)	0.0014
Breast	205 (4.16%)	201 (12.01%)	4 (0.12%)	<.0001
Prostate	112 (2.27%)	0 (0.00%)	112 (3.45%)	<.0001
Esophagus	83 (1.69%)	10 (0.60%)	73 (2.25%)	<.0001
Kidney and renal pelvis	60 (1.22%)	20 (1.20%)	40 (1.23%)	0.9157
Bladder	60 (1.22%)	10 (0.60%)	50 (1.54%)	0.0044
Stomach	57 (1.16%)	17 (1.02%)	40 (1.23%)	0.5056
Lip, oral cavity and pharynx	54 (1.10%)	13 (0.78%)	41 (1.26%)	0.1224
Ovary	50 (1.02%)	50 (2.99%)	0 (0.00%)	<.0001
Corpus uteri and uterus, part unspecified	33 (0.67%)	33 (1.97%)	0 (0.00%)	<.0001
Skin	31 (0.63%)	9 (0.54%)	22 (0.68%)	0.5599
Larynx	26 (0.53%)	5 (0.30%)	21 (0.65%)	0.1115
Cervix uteri	4 (0.08%)	4 (0.24%)	0 (0.00%)	0.0053
Data are displayed as number of deaths (%)				

Figure: (abstract: AS158)

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Background and Aims: Histological criteria used to diagnose and stage non-alcoholic fatty liver disease (NAFLD) have proven to be insufficient to predict time-dependent changes in fibrosis.[1] Only changes in disease activity have been reported to be associated with fibrosis progression in NAFLD. In this study we aim to explore predictors of NAFLD progression by combing histological, genetic and transcriptomics data in a large international cohort.
Method: The EuroDELTA cohort comprised patients from the European NAFLD Registry with two or more liver biopsies conducted at least one-year apart, without cirrhosis at baseline, that were identified at nine specialist centres across Europe. Samples were centrally read and histologically graded and staged using the NASH-CRN system. *PNPLA3* rs738409 and *TM6SF2* rs58542926 SNP genotypes were determined using TaqMan® probes on DNA from peripheral blood mononuclear cells. Targeted transcriptomics analysis was performed on mRNA isolated from a subset of formalin-fixed paraffin-embedded samples on the nanoString® nCounter analysis system using a custom-made assay panel. A selection of markers were validated on protein level using immunohistochemistry.
Results: A total of 517 patients with NAFLD were included with a mean age of 49 ± 12 years, a mean BMI of the cohort was 32.1 ± 6.0 Kg/m^2 and 63% were male. At baseline, 33% of the patients had T2DM and 47% had hypertension. During follow-up (median 4.8 (1–23.6) years), fibrosis progressed in 34% and regressed in 22%. Only the presence of type 2 diabetes at baseline was independently associated with fibrosis progression rate (OR 1.14). No single baseline histological feature, including ballooning, inflammation or NAFLD activity score, had sufficient precision to predict subsequent fibrosis progression. Carriage of the genetic variants *PNPLA3* rs738409 or *TM6SF2* rs58542926 did not confer to a significant predictive factor. In contrast, significant transcriptomic differences were observed at the mRNA level. At baseline, 117 differentially expressed genes predictive of subsequent disease progression were identified ($p < 0.05$): increased expression of genes correlating to "extracellular remodeling" (*LTBP2*, *COL1A1*, *COL4A2*, *ADAMTS2*, *LOXL4*, *STMN2*), "apoptosis" (*TP53I3*, *BCL2L1*) and cytokines/ligands (*GDF15*, *THY1*, *SPP1*/*OPN*). Interestingly, a reduction in expression of metabolism-related genes (*HSD17B13*, *ELOVL1*, *ACADSB*) and genes relating to coagulation (*F9*, *F10*) was observed. On protein level osteopontin (SPP1/OPN) positivity was observed in biliary epithelial cells, suggesting an immunoregulatory role.
Conclusion: This study provides novel insights into transcriptional changes during NAFLD evolution and fibrosis progression as well as proof of principle of a potential novel predictive transcriptomic "fingerprint" for disease progression.

AS160
A multidisciplinary approach to non-alcoholic fatty liver disease (NAFLD) improves cardiovascular risk factors

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Background and Aims: Cardiovascular (CV) disease is the leading cause of death in unselected patients with non-alcoholic fatty liver disease (NAFLD). Although the need of a multidisciplinary approach is highlighted in guidelines, there is lack of data to demonstrate its effectiveness. We assessed the efficacy of a multidisciplinary clinic through control of metabolic comorbidities and surrogate markers of liver involvement.
Method: Prospectively collected data of patients referred to a multidisciplinary NAFLD clinic, comprehensive of a hepatological consultation, cardiovascular risk assessment and dietetic counseling, were analyzed.
Results: 273 patients were enrolled (57% males) with a mean age of 56.4 ± 12.1 years. The median follow-up was 18 months. The prevalence of obesity, hypertension and diabetes was 60%, 67% and 50% respectively, while 13.2% had a positive history of CV events. At baseline, dyslipidaemia management was suboptimal in 64 patients (25.2%), while 57 (41.9%) patients with diabetes and 36 (19.6%) patients with hypertension needed modification of their treatment. During follow-up, there were statistically significant improvements in ALT ($p = 0.013$), AST ($p = 0.013$), systolic and diastolic blood pressure ($p = 0.002$ and 0.014 respectively), total cholesterol ($p < 0.001$) and glycated haemoglobin in diabetic patients (70.2 to 62.5 mmol/mol, $p = 0.04$). 142 patients (52%) achieved weight loss during the follow-up ($\geq 10\%$, $\geq 7\%$ and $\geq 5\%$ in 8.2%, 6% and 7.3% of the cohort respectively). The total number of patients with a QRISK3 score $\geq 10\%$ decreased from 156 (62.7%) to 97 (48.5%).
Conclusion: A multidisciplinary NAFLD approach was effective in improving liver-related and CV risk factors. A strong collaboration between primary and secondary care is essential to implement and maintain these improvements in the long term.

AS161
Active non-alcoholic steatohepatitis and severe fibrosis are associated to dysfunctional adipose tissue and worsen with adipose tissue insulin resistance independently of body mass index

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Background and Aims: Adipose tissue act as an endocrine organ that influences the metabolism by releasing adipokines, proinflammatory factors and free fatty acids (FFA), which contribute to insulin resistance (IR). Non-alcoholic fatty liver disease (NAFLD) occurs in the setting of IR due to increased delivery of free fatty acids (FFA) from peripheral lipolysis and de novo lipogenesis while clearance of hepatic FFA is through mitochondrial beta-oxidation, the dominant oxidative pathway, or by triglycerides (TG) secretion in plasma. We explored whether adipose tissue insulin resistance (adipo-IR, which measures the impaired suppression of lipolysis in the presence of high insulin levels), plasma FFA, TG and beta-hydroxybutyrate (BOH) (that reflects liver FFA oxidation) concentrations were associated to the severity of Non-alcoholic steatohepatitis (NASH).
Method: A large cohort of consecutively recruited patients with liver biopsy (n = 211, Body Mass Index (BMI) 25–40 kg/m^2) were included in the study and characterised for presence of glucose intolerance (IGT) or diabetes (T2D) by oral glucose tolerance test. We measured plasma FFA, BOH, lipid profile, Adipo-IR (FFAxInsulin) and fat distribution by CT. Data were analysed by logistic multivariable analysis (LMA) adjusted for age, BMI, presence of IGT/T2D and odd ratios (OR) were calculated.

Results: Liver histology was as follows: 55 no NAFLD, 34 non-alcoholic fatty liver (NAFL) and 122 NASH. TG (128 ± 5 vs 141 ± 8 vs 176 ± 7 mg/dL) and Adipo-IR (9.0 ± 0.7 vs 10.6 ± 1,1 vs 13.5 ± 0.9 mmol/l*pmol/l) increased ($p < 0.008$) from noNAFL, NAFL to NASH. Visceral fat was increased similarly in NAFL (218 ± 15 cm^2) and NASH (196 ± 6 cm^2) compared to noNAFL (139 ± 8 cm^2, $p < 0.0001$), while BMI, subcutaneous fat, BOH and FFA were similar in the 3 groups. Presence of NASH was associated with increased Adipo-IR (OR = 2.5, CI 1.5–4.5, p = 0.0005) after adjusting for age, BMI, IGT/T2D. In case of increased necro-inflammation (ie "active NASH," the sum of ballooning and lobular inflammation ≥ 3) the OR was 2.6 (CI 1.4–4.7, p = 0.003). There was no independent association of FFA, BOH or TG. Moreover, NASH with severe fibrosis (F2-F4) had a much higher Adipo-IR (18.7 ± 4.1 mmol/l*pmol/l) *vs* NASH F0–1 (12.2+0.7 mmol/l*pmol/l), NAFL (10.6 ± 1.1 mmol/l*pmol/l) and noNAFL (8.6 ± 0.8 mmol/l*pmol/l, $p < 0.001$). In NASH with severe fibrosis (F2-4) the association with Adipo-IR had an OR = 3.3 (CI 1.4–8.0, p = 0.003) adjusted for age, BMI, IGT/T2D.

Conclusion: Increased adipo-IR was significantly associated to presence of active NASH and severe fibrosis independently of BMI, showing the importance of dysfunctional adipose tissue as a main target in this disease.

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The clinical and patient reported outcomes (PROs) profile of patients with non-alcoholic fatty liver disease (NAFLD) from real-world practices varies across the world

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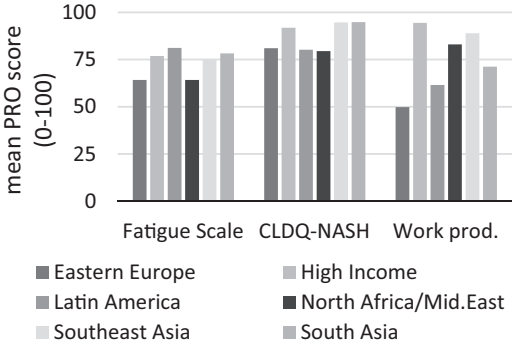
Background and Aims: NAFLD is a growing cause of chronic liver disease (CLD) worldwide. We assessed and compared clinical and PRO results in NAFLD patients enrolled in regions around the world to chronic viral hepatitis C (CVH).

Method: Global NAFLD/NASH Registry is enrolling NAFLD/NASH patients who are seen in real-world practices in 18 countries [6 Global Burden of Disease (GBD) super-regions]. Clinical and PRO data (CLDQ-NASH, FACIT-F, WPAI) are being collected. Similarly collected data from CVH patients were used for comparison.

Results: 7753 subjects (4250 NAFLD/NASH and 3503 CVH) were used for this analysis. In comparison to CVH, NAFLD/NASH patients were less likely males (44% vs. 52%), diabetics (37% vs. 13%) and have other components of metabolic syndrome (BMI 36 ± 10 vs. 27 ± 5, hypertension (HTN) 53% vs. 25%, hyperlipidemia (HL) 52% vs. 12%), with more depression and clinically overt fatigue (20% vs. 13% and 35% vs. 26%, respectively), but were less likely to have cirrhosis (8% vs. 14%) (all $p < 0.001$). Compared to CVH, PRO scores of patients with NAFLD/NASH were significantly impaired in all domains of FACIT-F and CLDQ (all $p < 0.05$, all but one $p < 0.01$); the greatest impairment was seen in Social Well-Being of FACIT-F, Activity/Energy, Abdominal Symptoms, Fatigue, and Systemic Symptoms of CLDQ (difference in group mean scores up to −8% of a PRO range size). Assessing geographic differences among NAFLD/NASH patients, 59% were enrolled from High-Income GBD super-region, followed by 14% in North Africa and Middle East, 12% in Southeast Asia, 8% in Latin America and the Caribbean, 4% in Eastern Europe, and 3% in South Asia. Clinical and PRO profile of NAFLD/NASH patients varied between the regions: patients were oldest in Eastern Europe (55 ± 11 years) and youngest in South Asia (44 ± 12), more likely males in Southeast Asia (62%) and less likely in Eastern Europe (26%). The highest BMI was in Eastern Europe (42 ± 9) and the lowest in South Asia (27 ± 4) along with the rates of type 2 diabetes (72% vs. 25%), HTN (90% vs. 27%), and HL (82% vs. 26%) in the same regions. The rates of psychiatric comorbidities (depression, anxiety) and fatigue were again the highest in Eastern Europe and the lowest in Southeast Asia (all $p < 0.0001$). Cirrhosis rate was the highest in South Asia (13%) and the lowest in Eastern Europe (1%) (all $p < 0.0001$). Assessment of PROs in NAFLD/NASH indicated the lowest CLDQ-NASH total scores were observed in Eastern Europe, Latin America, and North Africa/Middle East regions (4.9, 4.8, and 4.8 on a 1–7 scale, respectively); the highest were in Southeast and South Asia (5.7 in both regions). Similar trends were seen in PRO scores measured by FACIT-F and WPAI (all $p < 0.0001$) (Figure).



Conclusion: Patients with NAFLD/NASH have more comorbidities and PRO impairment than patients with CVH seen in real-world practices globally. Clinical and PRO presentations of NAFLD/NASH patients vary around the world.

Liver development and regeneration

AS163

Cholangiocyte organoids are plastic and their identity is controlled by their local microenvironment

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Background and Aims: The biliary tree is characterized by distinct populations with different susceptibility to disease. However, the characteristics and regenerative potential of these populations remain elusive. To address this challenge, we characterise the human intra- and extra-hepatic biliary epithelium using single-cell RNA sequencing (scRNAseq). We then explore which of these populations can be propagated as cholangiocyte organoids (COs) and interrogate the plasticity and the mechanisms controlling the identity of these organoids in vivo and in vitro.
Method: Biliary Epithelial Cells (BECs) from discarded donor livers and cholangiocyte organoids (COs) were characterized using droplet-encapsulation scRNAseq. (10 individuals, 14,003 primary cholangiocytes, 28,513 organoid cells, 12 lines). Pseudotime and Gene Ontology (GO) analysis was performed using Monocle and EnricR respectively. COs from different BEC populations were derived under the same culture conditions using our established technique. scRNAseq results were validated in human tissue though immunofluorescence. NOD-SCID mice were used for CO transplantation experiments.
Results: Our data identified transcriptional differences between intrahepatic (IHD), common bile duct (CBD) and gallbladder (GB) BECs. However, pseudotime analysis revealed a gradual transition in transcriptional signature between these populations. GO analysis identified differentially expressed genes as factors facilitating adaptation of cholangiocytes to their local microenvironment, such as bile modification genes. BECs cultured as COs assumed a similar profile, upregulated culture-condition associated genes and lost regional differences. IHD COs treated with gallbladder bile or Farnesoid X Receptor (FXR) agonists assumed a GB signature, while GB COs transplanted in the liver of immunocompromised mice assumed an IHD signature.
Conclusion: Our results provide the first transcriptional roadmap of the intra- and extrahepatic biliary tree; reveal the plasticity of BECs and COs and shed light into the mechanisms controlling their identity through FXR activation. These mechanisms could provide new insights into biliary regeneration and the effects of FXR agonists in cholestatic diseases.

AS164

Mapping origins of replication in a regenerating liver post partial hepatectomy

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Background and Aims: DNA replication begins at thousands of individual origins of replication (ORI) that are tightly regulated both spatially and temporally. Timely execution of replication and transcription is important to avoid DNA replication stress and collisions which could lead to genomic instability and mutagenesis. The aim of this study is to monitor DNA replication and transcription to determine if collisions between replication and transcription occur during the proliferative phase in a regenerating liver.
Method: We synchronized hepatocyte proliferation using two-thirds partial hepatectomy (PH) in mice. To map early S-phase replication origins, nascent DNA was labelled in vivo with EdU every 2 hours from 24 to 44 hours post resection with and without hydroxyurea (HU), to limit fork progression after origin firing. Edu containing DNA was sequenced from isolated hepatocytes. To label newly transcribed mRNA, EU was injected into mice between 24 and 40 hours in two hours intervals for 30 minutes before harvesting. EUseq was performed to identify nascent mRNA in vivo.
Results: We were able to map and identify the temporal pattern of ORI in hepatocytes following PH. Origins were located outside transcribed genes.
Conclusion: For the first time, we could show that in a normal regenerating liver, transcription and translation are synchronized and with no collisions happening between them.

AS165

Single cell RNA -seq atlas of a regenerating liver in mice reveals early Kupffer cell proliferation

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Background and Aims: Liver regeneration is initiated by loss of hepatic tissue to restore homeostatic levels of liver mass and function. The main mechanism is proliferation of parenchymal cells, nevertheless this complex and orchestrated process requires the coordination of multiple cell types in a spatially and temporally regulated manner. Using single cell RNA-seq, we reveal the cell specific contribution to early events during liver regeneration.
Method: Liver regeneration was initiated using a standard two-thirds partial hepatectomy (PHx) model in C57Bl/6 mice. Hepatic cells were isolated by a two-stage collagenase in situ digestion. scRNA-seq libraries were prepared from 5000 cells from sham control, 3 hours, 6 hours and 24 hours after PHx in duplicate. Liver cells were further characterized by mass cytometry, Kupffer cells (KC) proliferation was assessed by EdU incorporation and flow cytometry as well by spinning disk confocal intravital microscopy.

Results: We profiled the transcriptome of 11896 individual cells of the parenchymal and non-parenchymal fraction. scRNA-seq revealed early time regulation for endothelial cells, hepatocytes, bone marrow-derived macrophages (BMDM) and KC. Mass Cytometry identified changes in the number of B cells, Granulocytes and BMDM after PHx. Pathway enrichment analysis showed proliferation of KC at 24 h. This finding was validated by FACS sorting EdU postive cells in KC at 24 h and by in vivo imaging.
Conclusion: Our results provide a genome wide picture of liver regeneration at a single cell level and reveal the regulated genes in each cell population after partial hepatectomy. Additionally, we have shown for the first time in vivo Kupffer cells proliferation as the first cell to proliferate in the regenerating mouse liver following PHx.

AS166

Myeloid cell-specific deletion of ERK5 regulates the response to liver regeneration after partial hepatectomy (PH) in mice

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Background and Aims: The extracellular signal-regulated kinase 5 (ERK5) is a member of the Mitogen-Activated Protein Kinases family, and is involved in the modulation of proinflammatory mediators in endothelial cells and monocytes, and in the differentiation of monocytes to macrophages. In addition, signals derived from macrophages regulate liver regeneration after PH. We recently generated mice deletion of the ERK5 gene in cells of myeloid lineage (LysMCRE/ERK5KO).
This study was designed to investigate the phenotypic response of LysMCRE ERK5 KO mice subjected to PH.
Method: LysMCRE/ERK5KO mice were generated crossing ERK5 floxed mice (control mice) with mice expressing Cre-recombinase under the control of M-lysozyme promoter. Mice were subjected to a 65% partial hepatectomy (PH). Mice were sacrificed at 8, 24, 48 and 168 hours. Serum ALT and AST were measured using standard biochemical assays. Intrahepatic gene expression was assayed by quantitative real-time PCR.
Results: Measurement of liver-to body weight ratio showed that recovery of liver mass was slightly lower at 24 and 48 hours after PH in LysMCRE/ERK5KO mice, while no differences between the two experimental groups were observed at late time point (168 hours). Expression of the proliferation marker PCNA was decreased in LysMCRE/ERK5KO 48 hours after PH. Interestingly, although we did not observe a significant impairment of liver mass recovery in LysMCRE/ERK5KO mice, in these animals severe liver damage was evident at 24 and 48 hours after PH, as indicated by higher ALT and AST levels compared to the control group. Histological analysis confimed this result showing a higher degree of hepatic tissue damage in LysMCRE/ERK5KO mice subjected to PH. Analysis of M1/M2 markers in liver tissue showed a reduced expression of M2 markers (ARG1, MRC2), together with a parallel increase in M1 markers (CCL2, IL1β) in the LysMCRE/ERK5KO group 48 h after PH)+, compared to control mice.
Conclusion: This study suggests that ERK5 modulates the liver regeneration process regulating macrophage plasticity. Genetic loss of ERK5 in myeloid cells is associated with severe liver damage and reduced cell proliferation, a phenotype associated with enhanced M1 polarization of hepatic macrophage.

AS167

Ageing decreases the pool of newborn hepatocyte lineages, but does not impair their intrinsic proliferative response to partial hepatectomy in mice

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Background and Aims: Liver regeneration is known to decrease with age, but the operative mechanisms and the effects of aging on the sources of new hepatocytes are still unknown. Here, we evaluated the impact of aging on the contribution of newborn hepatocyte lineages to hepatocyte turn-over in the normal liver and after a partial hepatectomy (PH).
Method: The lineage reporter mT/mG mouse strain (Jackson Lab) was crossbred with mice expressing Cre-recombinase under the control of the Albumin promoter, generating litters (AlbCrexmT/mG mice) that expressed the Tomato-dye protein (mT+) in all cells, except in albumin-expressing cells which expressed EGFP (mG+) instead. Young adult (10–14 wk-o) and old (63–72 wk-o) male AlbCrexmT/mG mice underwent PH and were sacrificed 4 days later. Liver samples were formalin-fixed, sucrose-protected, and frozen in OCT. The contribution of intrahepatic albumin-naïve progenitor cells to the birth of *de novo* hepatocytes was evaluated by counting mT+ hepatocytes by confocal microscopy of thick liver tissue sections (300 micra) that had been made transparent using the CUBIC (Clear, Unobstructed Brain/Body Imaging Cocktails and Computational analysis) protocol. All counts were referred to the total number of hepatocytes evaluated in each mouse. A subset of mice underwent collagenase perfusions for hepatocyte isolation, and mT+ hepatocytes (negative for mG and F4/80, to correct for false positives) were counted by flow cytometry (FACS) and imaged after cell sorting.
Results: Compared with young adults, old mice showed a striking reduction of mT+ hepatocyte counts before (0.075% [0.023, 0.109] vs. 0.005% [0.001, 0.012], $p = 0.003$) as well as after PH (0.098% [0.051, 0.115] vs. 0.014% [0.002, 0.016], $p < 0.0001$). Such reductions resulted from a lower proportion of both isolated mT+ hepatocytes ($p < 0.0001$) and clusters of mT+ hepatocytes ($p < 0.01$). Despite these important differences, the fold-change increases of mT+ hepatocytes after PH was similar in both groups (Young: 1.378 [0.977, 1.378] vs. Old: 1.075 [0.941, 7.197], $p = 0.93$). Compared with baseline, PH increased the proportion of mT+ hepatocyte clusters (Young, $p = 0.0078$; Old, $p = 0.039$) and the percentage of mT+ hepatocytes localized in clusters (Young, $p = 0.008$; Old, $p = 0.039$) in both groups. The liver-to-body weight ratio tended to be lower in old mice after PH (3.15 [2.98, 3.57] vs. 2.95 [2.66, 3.29], $p = 0.11$). FACS and confocal microscopy of sorted mT+ hepatocytes confirmed the imaging counts.
Conclusion: Aging drastically decreases the birth of newborn hepatocyte lineages in mice. A considerable exhaustion of the pool of albumin-naïve intrahepatic progenitor cells rather than intrinsic defects of their proliferative capacity appeared to be the main operative mechanism. Increasing the endogenous pool of intrahepatic progenitors, therefore, could improve the liver regenerative capacity in advanced age.

AS168

Impaired hepatocyte cell division induces progenitor cell activation and emergence of bi-phenotypic hepatocytes

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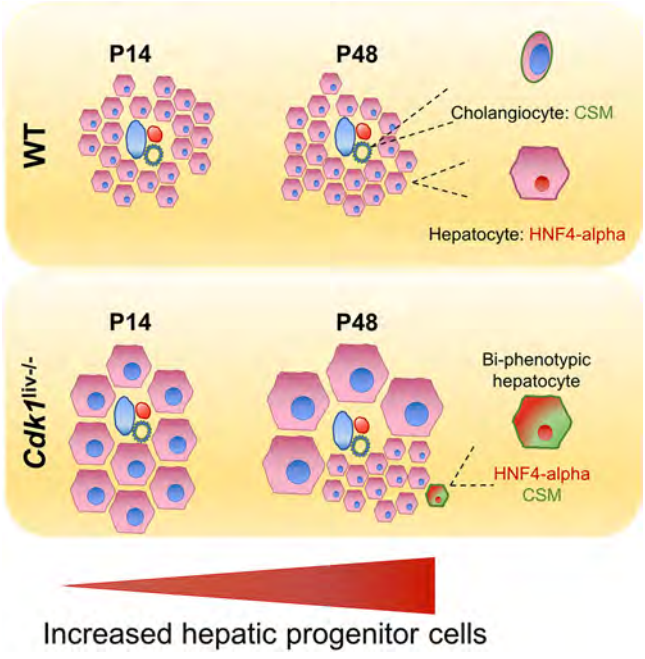
Background and Aims: Recent studies suggest the involvement of other cell types in liver regeneration upon impaired hepatocyte cell division. However, more investigation is needed on the source of these cells. We previously showed that deletion of *Cdk1*, a critical component of cell cycle, in hepatocytes (*Cdk1*$^{liv-/-}$) does not affect the development and the regeneration of the liver. However, excessive inflammation and fibrosis were observed during postnatal liver development. We detected hypertrophied hepatocytes accompanied by the emergence of normal sized hepatocytes (NSHs) that express CDK1, despite *Cdk1* being completely deleted at 2 weeks postpartum. This indicates a contribution of non-parenchymal cells to liver regeneration and development. Thus, our aim is to identify other cell types contributing to the regeneration of the liver in the absence of hepatocyte cell division.
Method: Liver samples were collected at three-day intervals from postnatal mice to identify important time points for the emergence of NSHs. AAV8-TBG-GFP tail-vein injection was used to label and track the fate of hepatocytes to show that NSHs are not emerging from pre-existing ones. Samples were analyzed via IHC, IF, qPCR, and WB. Hepatocyte isolation and FACS analysis were used for GFP labelled hepatocytes to identify and analyze bi-phenotypic hepatocytes.
Results: P37 and P48 *Cdk1*$^{liv-/-}$ liver displayed substantial amount of NSH populations near hypertrophied hepatocytes and they were localized around zone 1. We labelled both *Cdk1*$^{liv-/-}$ and WT mice with AAV8-TBG-GFP, which specifically infects hepatocytes and causes GFP expression. Samples were injected at P28 and harvested at P42. IHC and IF analysis revealed that in WT samples, all the hepatocytes retained GFP labelling as there is nearly no cell division after P28. However, in *Cdk1*$^{liv-/-}$ samples, only hypertrophied hepatocytes retained GFP labelling, while all the NSH populations were GFP negative. Additionally, IHC staining and WB analysis revealed that some of these NSHs were able to express CDK1. We identified a small number of normal sized HNF4-alpha^{+} hepatocytes that express a newly identified cholangiocyte specific marker (CSM) that also labels hepatic progenitor cells (HPCs). To analyze these bi-phenotypic hepatocytes, we labelled *Cdk1*$^{liv-/-}$ and WT mice with GFP and isolated hepatocytes three days later. FACS analysis of CSM and GFP revealed that 3.1% of the *Cdk1*$^{liv-/-}$ hepatocyte population display bi-phenotypic expression.



Conclusion: We demonstrated that compromised hepatocyte cell division activates HPCs during postnatal liver development. A small population of bi-phenotypic hepatocytes were identified, and further investigation is needed to elucidate the differentiation process and underlying signals that activate these bi-phenotypic cells.

Late Breaker: Orals

LBO01

Positive topline results from a 24-week, randomized, double-blind, placebo-controlled, multicenter, phase 2 study of the FGF19 analogue aldafermin (NGM282) in patients with non-alcoholic steatohepatitis

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Background and aims: Aldafermin (NGM282), an engineered FGF19 analogue, significantly inhibited bile acid synthesis, reduced hepatic fibrosis, inflammation and steatosis in previous 12-week NASH trials. Here we report the primary and key results from the 24-week (W24) study with paired liver biopsy.
Method: 78 subjects were randomized 1:2 to receive PBO (n = 25) or aldafermin 1 mg (n = 53) SC QD at 9 US study sites. Key inclusion criteria included biopsy-proven NASH with NAS≥4, stage 2–3 fibrosis and absolute liver fat content (LFC) ≥8%. Subjects underwent MRI-PDFF and liver biopsies at baseline (BL) and W24. The primary endpoint was change from BL to W24 in LFC. Histological endpoints included improvement in liver fibrosis by ≥1 stage with no worsening of NASH and resolution of NASH with no worsening of fibrosis (NASH CRN criteria).
Results: At W24, treatment with aldafermin resulted in statistically significant reductions in LFC (Table 1). A greater proportion of subjects on aldafermin achieved fibrosis reduction of ≥1-stage without NASH worsening (38% [aldafermin] vs 18% [PBO]), and NASH resolution with no worsening of fibrosis (24% [aldafermin] vs 9% [PBO]). 22% (aldafermin) vs. 0% (PBO) of subjects achieved both histological endpoints (P = 0.015). ALT, AST and fibrogenesis biomarkers (Pro-C3 and ELF) declined rapidly and significantly from BL with aldafermin therapy. AEs were mostly mild and moderate in severity. No difference in gastrointestinal AE was observed between arms. Incidences of SAEs were 12% (PBO) vs 4% (aldafermin), and discontinuations due to AE 4% (PBO) vs 0% (aldafermin). All SAEs were unrelated to drug.

Table 1: Change from baseline to week 24 in key endpoints

	PBO (n = 25)	Aldafermin 1 mg (n = 52)
Primary Endpoint		
Δ Absolute MRI-PDFF, %	−2.7 (1.3)	−7.7 (0.8) P = 0.002 vs PBO
% subjects with ↓5% absolute	*24%*	*68%* P < 0.001 vs PBO
Δ Relative MRI-PDFF	−13.1%	−38.8% P = 0.008 vs PBO
% subjects with ↓30% relative	*29%*	*66%* P = 0.004 vs PBO
Secondary Endpoints		
% Subjects achieving fibrosis improvement (≥1-stage) with no worsening of NASH	*18%*	*38%*
% Subjects achieving resolution of NASH with no worsening of fibrosis	*9%*	*24%*
% Subjects achieving fibrosis improvement (≥1-stage) with no worsening of NASH AND resolution of NASH with no worsening of fibrosis	*0%*	*22%*
Δ Absolute ALT, U/L	−15.9 (3.5)	−36.6 (2.4)
Δ Absolute AST, U/L	−8.5 (3.6)	−19.0 (2.4)
Δ Pro-C3, ng/mL	−0.9 (1.1)	−5.5 (0.7)

Shown are LS mean (SE) or %subjects.

Conclusion: In patients with NASH, aldafermin therapy resulted in statistically significant reduction in LFC and robust improvement in fibrosis and NASH histology compared with PBO. A greater proportion of patients treated with aldafermin achieved both histological endpoints of fibrosis improvement and NASH resolution compared to PBO. Aldafermin 1 mg maintained a durable response for 24 weeks with a favorable tolerability and safety profile.

LBO02

ATTIRE: Albumin to prevent infection in chronic liver failure: an interventional randomised controlled trial

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Background and aims: Acutely decompensated cirrhosis patients are highly prone to infection. Multiple experimental studies support an anti-inflammatory role for Albumin in addition to its oncotic properties. Evidence supports the use of weight-based infusions of 20% Human Albumin Solution (HAS) for Spontaneous Bacterial Peritonitis and Hepato-renal syndrome, but albumin is also widely used for other indications where there is an absence of trial data. Recent albumin trials in outpatients with ascites support the notion that regimens that aim to normalise serum albumin concentrations might improve mortality. The ATTIRE trial aimed to determine if targeting a serum albumin level ≥35 g/L in decompensated cirrhosis inpatients using repeated daily HAS infusions reduced incidence of infection, renal dysfunction and mortality compared to standard care.
Method: ATTIRE was a multicentre, open label trial in hospitalised decompensated cirrhosis patients with serum albumin <30 g/L at enrollment at 35 UK sites (January 2016–June 2019). Treatment commenced within 3 days of admission with patients randomised to targeted 20% HAS for up to 14 days (or discharge) or standard care. The composite primary endpoint was new infection, renal dysfunction or mortality from day 3–15 of treatment.
Results: 828 patients were recruited with no baseline differences between groups with respect to median(IQR): creatinine 68(54–90) μmol/L, bilirubin 94(46–171) μmol/L, INR 2(1–2) and albumin 23(4) g/L. 70% were male, 79% reported alcohol misuse, 28% had infection and 53% were prescribed antibiotics. The median(IQR) volume of HAS infused to patients in the treatment versus standard care arm was 1000(700–1500) ml vs 100(0–600) ml (p < 0.0001). There was no difference in composite primary endpoint between targeted albumin (n = 125/414; 30.2%) and standard care (n = 128/414, 30.9%, OR 0.968 (95%CI 0.716–1.307, p = 0.830). There was no difference when the endpoint window was extended to day 1, in individual components, length of stay or mortality at 3/6 months. There was no treatment effect in subgroup analyses that included baseline organ dysfunction, infection, MELD score, albumin level or reason for admission. The mean increase in cost associated with intervention was £573.26 (95% CI −1,247.54–101.01). There were more serious adverse events in the HAS arm (95 vs 74).
Conclusion: The ATTIRE trial does not support targeted HAS over current UK standard care for hospitalised decompensated cirrhosis patients.

LBO03

Early liver transplantation for severe alcoholic hepatitis not responding to medical treatment: results of the French-Belgian prospective study QuickTrans

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Table: (abstract: LBO02)

		Albumin	Standard Care	Adjusted OR (95% CI)	p
		n = 414	n = 414		
Primary outcome	n (%)	125 (30.2%)	128 (30.9%)	0.968 (0.716–1.307)	0.830
Composite endpoint components (day 3–15):					
New infection		87 (21.0%)	76 (18.4%)	1.196 (0.845–1.693)	0.313
Renal dysfunction		45 (10.9%)	62 (15.0%)	0.674 (0.445–1.022)	0.063
Death		32 (7.7%)	34 (8.2%)	0.936 (0.566–1.550)	0.798
3-month mortality		84 (20.3%)	80 (19.3%)	1.084 (0.761–1.544)	0.6548

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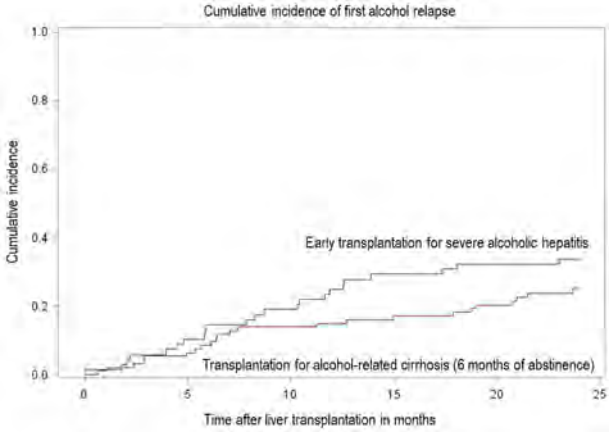
Background and aims: Early liver transplantation (eLT) for severe alcoholic hepatitis (SAH) is an emerging therapy that must be evaluated in prospective controlled studies with a rigorous study design to bring reliable data to experts.
Method: this prospective controlled trial (NCT01756794) compared 3 groups: A: patients with SAH not responding to medical treatment selected for eLT using a dedicated score (≥220/250), based on social and addiction parameters; B: patients candidates for transplantation for alcohol-related cirrhosis with at least 6 months of abstinence; C: patients with SAH not responding to medical treatment denied for eLT (score <220). Primary analysis was restricted to transplanted patients, to assess the non-inferiority of A versus B on 2-year alcohol relapse after LT using the alcohol timeline follow back (ATLFB) method and a pre-specified margin of 10%. Secondary outcomes were pattern of alcohol relapse and survival after LT. A secondary analysis was restricted to all patients of groups A and C to assess the benefit of eLT in SAH on 2-year survival.
Results: We included 155 patients with SAH: 78 selected for eLT (group A, median Lille score = 0.86), 77 denied for eLT (group C, median Lille score = 0.81). 129 patients were included in group B. Primary analysis: 68 (A) and 93 patients (B) were transplanted and included. MELD score at inclusion in groups A and B were 30.6 vs. 22.3, p < 0.001. The non-inferiority of A versus B was not demonstrated with a 2-year alcohol relapse of 33.8 (A) and 24.7% (B, figure), absolute difference of 9.1, one-sided 95% confidence interval, −∞ to 21.1%. Regarding secondary outcomes, 2-year heaving drinking relapse rate was higher in group A (22.1 vs. 5.4%, p < 0.001). In heavy drinking relapsers, median percentage of time spent to drink during the follow-up was 10 (A) vs. 5.9% (B). Two-year survival in groups A and B was similar (89.7 vs. 88.1%). Secondary analysis: 2-year survival was higher in group A (patients transplanted or not, n = 78) than in group C (n = 77): 82.8 vs. 28.2%, p < 0.001.



Conclusion: In the first controlled study in this field, relapse rate is of 33.8% in patients early transplanted for SAH as compared to 24.7% in patients with alcohol-related cirrhosis. Using a pre-specified non-inferiority margin of 10%, we cannot conclude to non-inferiority. Heavy drinking is more frequently seen after eLT. Early liver transplantation induces a drastic improvement of survival in patients with SAH not responding to medical therapy.

LBO04

Safety and efficacy of combination therapies including cilofexor/firsocostat in patients with bridging fibrosis and cirrhosis due to NASH: Results of the phase 2b ATLAS trial

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Background and aims: Patients with advanced fibrosis due to NASH are at increased risk of end-stage liver disease, hepatocellular carcinoma, and mortality. We evaluated the safety and efficacy of an ACC inhibitor, FXR agonist, and ASK1 inhibitor, as monotherapy and in combination, in patients with advanced fibrosis due to NASH.
Method: In this phase 2b trial, 392 patients with advanced fibrosis (F3-F4) due to NASH were randomized to receive placebo, selonsertib 18 mg (SEL), cilofexor 30 mg (CILO), or firsocostat 20 mg (FIR), alone or in two-drug combinations, once daily for 48 weeks (W48). Biopsies from baseline (BL) and W48 were read by a central reader and digital images of biopsies were evaluated using a machine learning (ML) approach (PathAI, Boston, MA). The primary endpoint was the proportion of patients with a ≥1-stage improvement in fibrosis without worsening of NASH. Secondary endpoints included changes in NAFLD Activity Score (NAS), liver biochemistry, and noninvasive fibrosis markers.
Results: The majority of patients had cirrhosis (56%), diabetes (72%), and NAS ≥5 (83%). More patients treated with combination therapy achieved a ≥1-stage improvement in fibrosis without worsening of NASH compared to placebo: CILO/FIR (21%, p = 0.17), CILO/SEL (19%, p = 0.26), FIR/SEL (15%, p = 0.62), FIR (12%, p = 0.94), CILO (12%, p = 0.96), and placebo (11%). Based on a ML approach, CILO/FIR led to a significant decrease in NASH CRN fibrosis score (difference in LSmeans from BL to W48: −0.42 vs. −0.16 for placebo; p = 0.040) and a shift in biopsy proportionate area from F3-F4 to ≤F2 fibrosis. Compared to placebo, CILO/FIR led to significantly increased proportions of patients with a ≥2-pt reduction in NAS and ≥1-grade improvements in steatosis, lobular inflammation, and ballooning (all p < 0.05; Figure). Fibrosis improvement without worsening of NASH with CILO/FIR was more frequent in patients with ≥2-pt NAS response (35% vs 14%, p = 0.060). CILO/FIR also led to significant improvements

in serum ALT, AST, bilirubin, total bile acids, CK18, insulin, estimated glomerular filtration rate (eGFR), and ELF score (all $p \leq 0.05$), and an increase in the proportion of patients with ≥25% reduction in liver stiffness by transient elastography (45% vs 20% with placebo, p = 0.016). All regimens were well tolerated. Pruritus occurred in 28% of patients treated with CILO/FIR (73% mild; no Grade 3 or discontinuations) vs 15% with placebo. LSmean changes in lipids vs placebo in patients treated with CILO/FIR were: total cholesterol (+17 mg/dL, p = 0.005), LDL (+9 mg/dL, p = 0.080), HDL (−4 mg/dL, p = 0.012), and triglycerides (+45 mg/dL, p < 0.001).

Conclusion: In patients with bridging fibrosis and cirrhosis, treatment with CILO/FIR for 48 weeks was well tolerated and led to improvements in fibrosis and NASH activity. This combination offers the potential for fibrosis regression in patients with advanced fibrosis due to NASH.

LBO05

Genome-wide association study for alcohol-related cirrhosis identifies new risk loci in MARC1 and HNRNPUL1

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Background and aims: The host genetics underpinning the development of alcohol-related liver cirrhosis is beginning to emerge, but is still incompletely understood. Better insight would improve risk-stratification of patients, help delineate its pathophysiology, and support the development of new treatments. The UK Biobank (UKB) study integrates host genotyping and health behavior data for a cohort of half a million individuals in UK aged 40–69 years, with available data for a wide range of biochemistry variables. The aim of this study was to use this resource to undertake a Genome-Wide Association Study (GWAS) for alcohol-related liver disease.

Method: UKB participants consuming >25 units/week of alcohol if female and >36 units/week if male, were included in a discovery GWAS against indirect markers of hepatic fibrosis and hepatocellular injury; *viz*. APRI, FIB-4, the Forn's score, serum alanine and aspartate transaminase.

Loci identified in the discovery analysis were then tested for association with alcohol-related cirrhosis status in a previously generated European GWAS data-set, together with a nested alcohol-related cirrhosis case-control study derived from within UKB (Phase 1 validation). Variants associated with alcohol-related cirrhosis in Phase 1 validation at a False Discovery Rate (FDR) <20%, were then

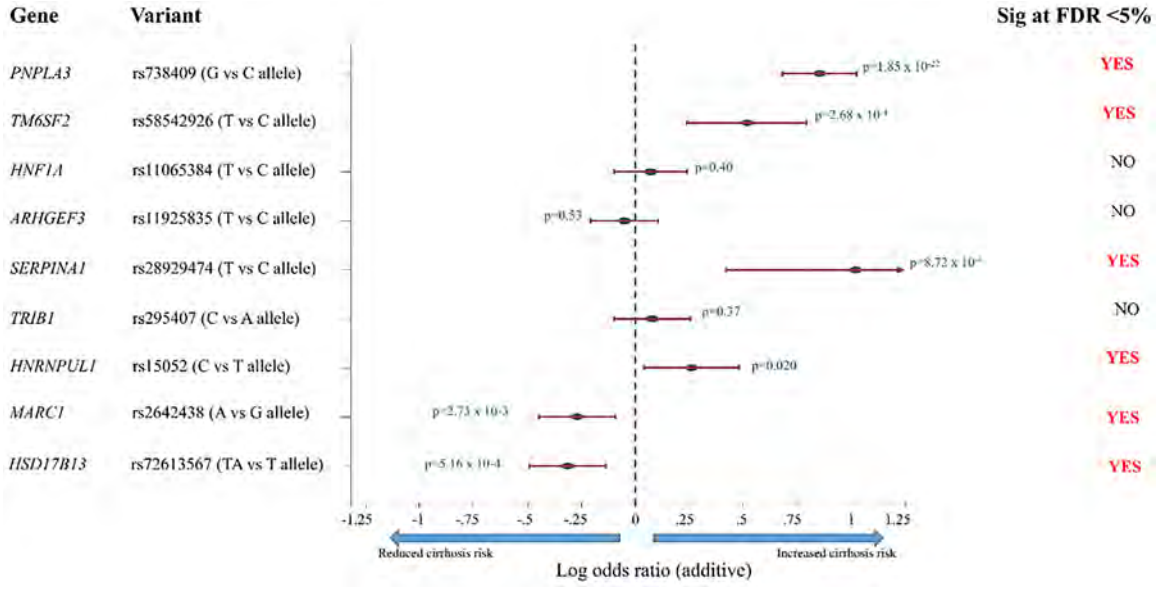

Figure: (abstract: LBO05): Results of phase 2 replication analysis. Association are adjusted for age, sex, type 2 diabetes and BMI.

directly genotyped in two European validation cohorts comprising 1536 cases with alcohol-related cirrhosis and 771 alcohol misusers without liver disease (Phase 2 validation). A FDR <5% was used to judge statistical significance in phase 2 validation, adjusting for age, sex, type 2 diabetes and BMI.

Results: The discovery GWAS, which included 35,839 UKB participants, identified 50 independent risk loci with genome-wide significance (p-value $<5 \times 10^{-8}$). Nine of these loci were significantly associated with risk of developing alcohol-related cirrhosis in the Phase 1 validation; six of the nine loci were significantly associated with risk of developing alcohol-related cirrhosis in the Phase 2 validation (see Figure). These six included four known risk variants in *PNPLA3*; *TM6SF2*; *HSD17B13*; and *SERPINA1*, plus two novel risk variants in *mitochondrial amidoxime reducing component 1* (*MARC1)* and *heterogeneous nuclear ribonucleoprotein U like 1 (HNRNPUL1)*. The minor "A" allele of *MARC1*:rs2642438 was associated with a reduced risk of cirrhosis (adjusted OR: 0.76; p = 0.0027); conversely the minor "C" allele of *HNRNPUL1*:rs15052 was associated with an increased risk (adjusted OR:1.30; p = 0.020).

Conclusion: This new GWAS has identified two novel single nucleotide polymorphisms (SNPs) – *MARC1*:rs2642438 and *HNRNPUL1:*rs15052 – that modulate the risk of alcohol-related cirrhosis in opposite directions. Both variants warrant further investigation.

LBO06

Response to discontinuation of long-term nucleos(t)ide analogue treatment in HBeAg negative patients: Results of the Stop-NUC trial

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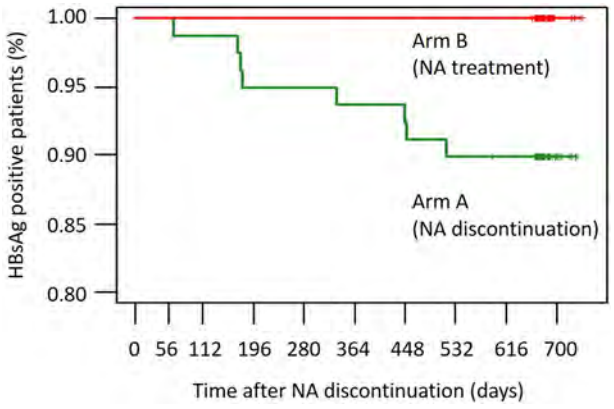
Background and aims: Disc Discontinuation of long-term suppression of HBV replication with nucleos(t)ide analogues (NUCs) can result in durable immune control of hepatitis B virus (HBV) replication in HBeAg negative patients. We have assessed the effect of NUC discontinuation in HBeAg negative patients in a prospective, multicenter, randomized trial (the Stop-NUC study).

Method: HBeAg-negative patients without cirrhosis who had achieved suppressed HBV DNA for ≥4 years during NUC therapy were randomly assigned to either stop (Arm A) or continue (Arm B) treatment. The primary endpoint was sustained HBsAg loss at week 96. Secondary end points included HBsAg seroconversion, virologic response (HBV DNA ≤20 IU/mL), biochemical response (alanine aminotransferase (ALT) < upper level normal (ULN)) as well as number of ALT flares (ALT >3 ULN) and time to re-therapy in the non-treatment arm. All patients were observed for 96 weeks, with visits including standard laboratory tests including HBV DNA levels, quantitative HBsAg, alanine aminotransferase (ALT) and bilirubin measurements, and adverse event reporting. In each arm 83 patients were randomized. The full analysis set comprised 158 patients (79 vs 79), excluding eight patients who dropped out immediately after randomization.

Results: At week 96 after NUC discontinuation, HBsAg loss or seroconversion were achieved in 8/79 (10%) and 6/79 (8%) patients in Arm A and in no patient in Arm B, respectively (p = 0.006 and p = 0.028). After NUC discontinuation, all patients in Arm A and no patient in Arm B experienced an HBV DNA flare >20 IU/mL, however, at week 96 HBV DNA were levels ≤20 IU/mL in 24/79 (31%) patients in Arm A and in all patients in Arm B (p < 0.001). ALT flare occurred in 28/79 (35%) patients in Arm A and in no patient in Arm B, and ALT levels were within normal ranges in 69/79 (88%) patients in Arm A and in 77/79 (97%) patients in Arm B at week 96 (p = 0.032). At week 96, NUC treatment had to be re-installed in 11/79 (14%) in Arm A while 54/79 (68%) patients had no indication for treatment according to current EASL recommendations. No patient in Arm A suffered serious adverse event possibly related to NUC discontinuation.



Conclusion: This first large-scale randomized study demonstrates the potential of discontinuation of long-term NUC treatment for induction of durable immune control and functional cure in patients with HBeAg negative chronic hepatitis B (EudraCT-Nr.: 2013-004882-15).

LBO07

Proton beam radiotherapy versus radiofrequency ablation treatment in patients with recurrent hepatocellular carcinoma: a randomized controlled phase 3 non-inferiority APROH trial

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Background and aims: Radiofrequency ablation (RFA) is the standard of care for patients (pts) with Barcelona Clinic for Liver Cancer stage 0 and A hepatocellular carcinoma (HCC) not suitable for surgery. The role of external proton beam radiotherapy (PBT) is under investigation and a phase 2 study of PBT showed promising local control and safety. Herein, we conducted an investigator-initiated phase 3 non-inferiority trial to evaluate the effects of PBT on recurrent or residual HCC (rHCC).

Method: Patients (pts) with rHCC (size <3 cm, number ≤2) were randomly assigned (1:1) to receive PBT (Arm P) or RFA (Arm R) according to the Child-Pugh score and initial tumour stage. If the randomly assigned method was not technically feasible, pts were allowed to enroll in the other arm. Eligible pts of Arm P received a total of 66 Gray equivalent in 10 fractions and those of Arm R received RFA with a monopolar electrode. The primary endpoint was 2-year (y) local progression-free survival (LPFS) rate with a non-inferiority margin of 15%; secondary endpoints included overall survival, progression-free survival, tumour response rate and safety profile. (NCT01963429).

Results: Between December 2013 and December 2017, 144 pts in Arm P (n = 72) and Arm R (n = 72) comprised the intention-to-treat (ITT) population and the trial was concluded on January 2020. The baseline characteristics of pts were well balanced. In Arm P, six pts switched to Arm R and five pts received another treatment, while in Arm R, 19 pts switched to Arm P and three pts received another treatment. Thus, the per-protocol (PP) population comprised 80 pts in Arm P and 56 pts in Arm R. In the ITT population, the 2-y LPFS rate with PBT vs. RFA was 92.8% vs. 83.2% (90% confidence interval [CI], 0.7–18.4%; p < 0.001), meeting criteria for non-inferiority. In the PP population, 2-y LPFS rate with PBT vs. RFA was 94.8% vs. 83.9% (90% CI, 1.8–20.0%; p < 0.001). The 3- and 4-y LPFS rate with PBT were also significantly non-inferior to those with RFA. Efficacy outcomes are shown in the figure. The most common any-grade adverse events (AEs) were radiation pneumonitis (32.5%), and decrease in leukocyte counts (23.8%) in Arm P; and increase in alanine aminotransferase level (96.4%), abdominal pain (30.4%) in Arm R. No Grade 4 AEs or mortality were noted.

Conclusion: PBT was non-inferior to RFA in terms of LPFS in pts with rHCC, and PBT was tolerable and safe, consistent with the known profile.

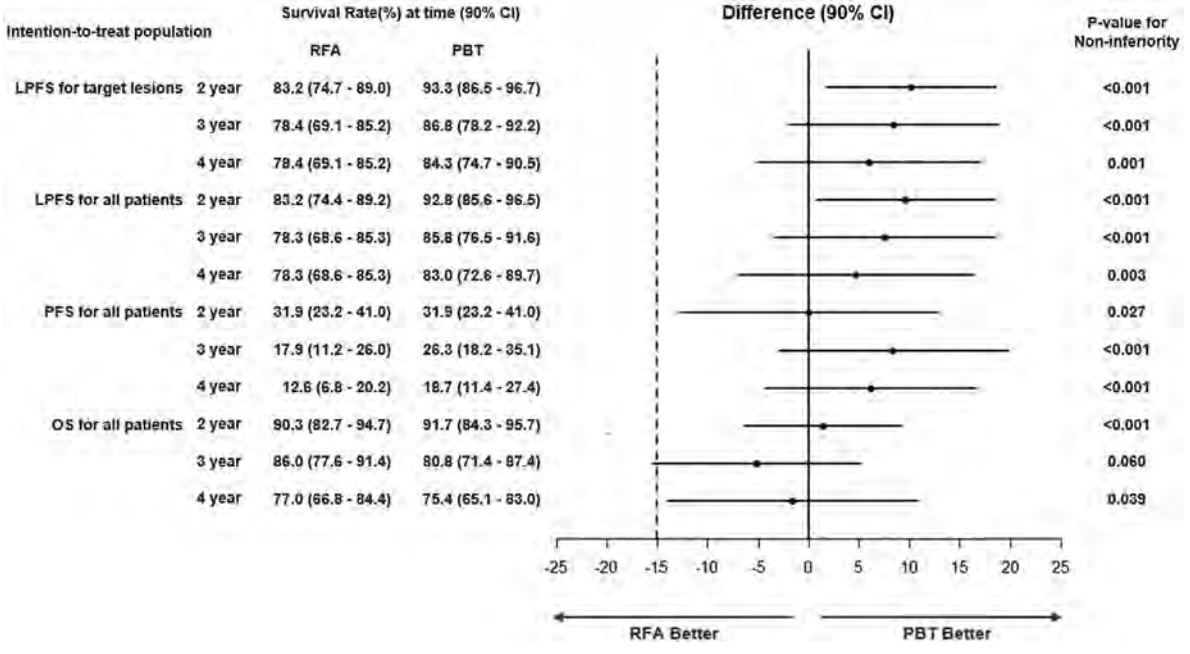

Figure: (abstract: LBO07)

LBO08

Serum bile acid control in long-term maralixibat-treated patients is associated with native liver survival in children with progressive familial intrahepatic cholestasis due to bile salt export pump deficiency

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Background and aims: Children with progressive familial intrahepatic cholestasis (PFIC) due to bile salt export pump (BSEP) deficiency often present with debilitating pruritus, short stature, and progressive liver disease. The NAPPED study (NCT03930810) shows that ~50% of patients receive a liver transplant by age 10, but those who achieve serum bile acid (sBA) levels of <100 μmol/L after partial external biliary diversion show improved native liver survival and reductions in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin. Maralixibat (MRX) is an apical sodium-dependent bile acid transport inhibitor that interrupts the enterohepatic recirculation, reducing pruritus and cholestasis, and improving growth at Week 72 in an open-label, long-term study (INDIGO; NCT02057718). Here, we describe >4.5 years of treatment with MRX.
Method: MRX was dosed at 280 micrograms/kg daily for 48 weeks, increasing to 280 micrograms/kg twice daily in the extension. The NAPPED sBA threshold (≤100 micromol/L) was applied to patients remaining on-study >4.5 years. Transaminases, bilirubin, and growth were assessed to Week 237.
Results: Of the enrolled patients (n = 19) with nontruncated BSEP mutation (median age 4.1 years, range 1–13; 32% male), 7 achieved sBA control and remained on-study as of Week 237. Mean (standard error) sBA reduction was 234.4 (80.5) micromol/L ($p < 0.05$) with a mean value of 44.2 (38.8) micromol/L (*vs.* 299.6 micromol/L at baseline [BL]). Mean reductions in AST and ALT were 35.4 (11.5) and 41.1 (14.3) U/L with mean values of 26.7 (*vs.* 62.1 at BL) and 16.7 (*vs.* 57.9 at BL), respectively (both $p < 0.05$). Mean reductions in total and direct bilirubin were 0.1 (0.3) and 0.4 (0.2) mg/dL with mean values of 0.7 (*vs.* 0.8 at BL) and 0.1 (*vs.* 0.6 at BL), respectively ($p = 0.8$ and 0.13). Those with abnormal bilirubin, normalized. No ongoing patients were listed for liver transplant after >4.5 years of MRX. Growth (height z-score; $p < 0.01$) and pruritus ($p < 0.001$) improved significantly. Long-term MRX was safe and well tolerated; the most frequent treatment-emergent adverse events were mild to moderate in severity.
Conclusion: Patients who achieved control of sBA during MRX treatment had native liver survival beyond 4.5 years, improved liver biochemistry and improved growth, suggesting the disease-modifying potential of MRX. These data support MRX as a potential alternative to surgery for children with PFIC due to nontruncating BSEP deficiency.

LBO09

A phase 1b study of lenvatinib plus pembrolizumab in unresectable hepatocellular carcinoma

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Background and aims: Lenvatinib (LEN), a multikinase inhibitor of vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor alpha, RET, and KIT, is approved for first-line (1L) treatment of unresectable hepatocellular carcinoma (uHCC). The US FDA granted accelerated approval to pembrolizumab (PEMBRO), an antiprogrammed death receptor-1 monoclonal antibody, for patients (pts) with HCC after sorafenib therapy. We assessed the safety and efficacy of LEN + PEMBRO in the first 80 pts with uHCC enrolled in the 1L setting.
Method: In this phase 1b trial (NCT03006926), pts received LEN 12 mg/day (bodyweight [BW] ≥60 kg) or 8 mg/day (BW <60 kg) orally + PEMBRO 200 mg intravenously on day 1 of a 21-day cycle. Primary endpoints were safety and tolerability for Part 1, and objective response rate (ORR) and duration of response (DOR) by modified Response Evaluation Criteria In Solid Tumors (mRECIST), and RECIST version 1.1 per independent imaging review in the 1L setting for Part 2.
Results: No dose-limiting toxicities were found in Part 1 (6 pts). At data cutoff (October 31, 2019), the first 80 pts enrolled in the 1L setting had a median follow-up of 11.5 months; the median duration of treatment was 8.5 months (LEN, 8.3 months; PEMBRO, 7.7 months), and 26 pts continued treatment (LEN only, n = 2; both drugs, n = 24). Median overall survival was 22.0 months (95% CI 14.6–not estimable). Tumor responses assessed by mRECIST per investigator assessment are reported herein. Median progression-free survival was 8.6 months (95% CI 6.9–9.7) and ORR was 43.8% (95% CI 32.7–55.3); 5.0% of pts had a complete response and 38.8% of pts had a partial response. Median DOR was 12.6 months (95% CI 6.5–18.7), median time to response was 2.4 months (range: 1.2–11.8) and disease control rate (complete response + partial response + stable disease [≥5 weeks]) was 83.8% (95% CI 73.8–91.1). 21.3% of pts discontinued LEN + PEMBRO due to an adverse event (AE). Treatment-related AEs (TRAEs) occurred in 95% of pts (grade ≥3,

68%; grade ≥4, 5%). 35% of pts had serious TRAEs and 3 pts died from a TRAE (1 each for: acute respiratory failure/acute respiratory distress syndrome, intestinal perforation, abnormal hepatic function).
Conclusion: LEN + PEMBRO has promising antitumor activity with a tolerable safety profile. An ongoing phase 3 trial (NCT03713593) is assessing LEN + PEMBRO vs LEN alone as 1L therapy for uHCC.

LBO10
Atezolizumab + bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma: safety results from the Phase III IMbrave150 study

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Background and aims: In IMbrave150, atezolizumab (atezo)+bevacizumab (bev) demonstrated a statistically significant and clinically meaningful improvement over sorafenib (sor) for the co-primary endpoints of overall survival (OS; HR 0.58 [95% CI, 0.42–0.79; p = 0.0006]) and independent review facility-assessed progression-free survival (PFS) per RECIST 1.1 (HR 0.59 [95% CI, 0.47–0.76; p < 0.0001]) in 501 patients (pts) with unresectable hepatocellular carcinoma (HCC) who had not received prior systemic therapy (tx) (Cheng ESMO Asia 2019). Here, we report safety data from IMbrave150 (NCT03434379).
Methods: In this open-label study, pts with systemic-tx naïve, unresectable HCC were randomised 2:1 to receive either atezo 1200 mg intravenously (IV) every 3 weeks (q3w) + bev 15 mg/kg IV q3w or sor 400 mg twice daily until unacceptable toxicity or loss of clinical benefit per investigator. Adverse events (AEs) were assessed per CTCAE version 4.0. AEs of special interest (AESI) were sponsor-defined based on the immune-mediated risks of atezo and other drugs in its class.
Results: In the safety population, 329 pts received atezo+bev and 156 received sor. Median tx duration was 7.4 mo for atezo, 6.9 mo for bev and 2.8 mo for sor (all ranges, 0–16 mo). Grade (Gr) 3–4 AEs occurred in 57% of pts receiving atezo+bev and 55% of pts receiving sor. Gr 5 AEs occurred in 5% and 6% of pts, respectively. AEs led to discontinuation of both atezo+bev in 7% of pts and of sor in 10% of pts. In both arms, most AESIs were Gr 1–2. Gr 3–4 atezo AESIs occurred in 26% and 30% of the atezo+bev and sor arms, respectively. More pts receiving atezo+bev (12%) required corticosteroid treatment than with sor (3%). The rate of immune-mediated hepatitis was comparable between the atezo+bev and sor arms (43% vs 40%, respectively).
Conclusions: Atezo+bev was generally well-tolerated in pts with HCC, and potential immune-mediated AESIs, a toxicity concern with checkpoint inhibitors, were manageable. The safety profile was consistent with the known risks of the individual study tx and underlying disease. The positive efficacy and patient-reported outcomes from IMbrave150 and these safety findings suggest that atezo +bev should be considered a practice-changing tx for pts with unresectable HCC who have not received prior systemic tx.

LBO11
Nivolumab + ipilimumab combination therapy in patients with advanced hepatocellular carcinoma: subgroup analyses from CheckMate 040

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Background and aims: Nivolumab (NIVO) monotherapy is approved in the United States and other countries for patients with hepatocellular carcinoma (HCC) treated with sorafenib (SOR) based on CheckMate 040 (NCT01658878), which reported 14% objective response rate (ORR) and 16-month median overall survival (mOS; El-Khoueiry et al. Lancet 2017). Primary efficacy and safety of NIVO + ipilimumab (IPI) in patients with advanced HCC previously treated with SOR were presented recently (Yau et al. J Clin Oncol 2019). We will present subgroup analyses from this study.
Method: Patients were randomized to 3 arms: [A] NIVO 1 mg/kg + IPI 3 mg/kg Q3W (4 doses) or [B] NIVO 3 mg/kg + IPI 1 mg/kg Q3W (4 doses), each followed by NIVO 240 mg Q2W, or [C] NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W. Treatment continued until intolerable toxicity or disease progression. Primary endpoints were safety/tolerability, ORR, and duration of response (DOR; investigator assessment per RECIST v1.1). Key secondary endpoints included disease control rate (DCR), OS, and progression-free survival (blinded independent central review [BICR] per RECIST v1.1); key exploratory endpoints included ORR (BICR per RECIST v1.1). Data cutoff was January 2019.
Results: A total of 148 patients were randomized. Minimum OS follow-up from last patient randomization date to data cutoff was 28 months. At baseline, 34% of all patients had vascular invasion, 82% had extrahepatic spread, and 91% had Barcelona Clinic Liver Cancer stage C; 84% discontinued SOR because of disease progression and 14% because of toxicity. For all treated patients, ORR was 31% (7 had complete response), with median DOR of 17 months; DCR was 49%; the 30-month OS rate was 37%. NIVO + IPI was well tolerated; 38% of patients had grade 3–4 treatment-related adverse events (TRAEs; most common any grade: pruritus and rash; most common grade 3–4: aspartate aminotransferase increase and lipase increase); 5% had grade 3–4 TRAEs leading to discontinuation. Subgroup analyses based on duration of prior SOR therapy and other patient characteristics will be presented.

Conclusion: NIVO + IPI led to clinically meaningful benefits, with a manageable safety profile in patients previously treated with SOR. NIVO + IPI may provide a new treatment option for these patients.

LBO12

Data from the third dose cohort of an ongoing study with ADP-A2AFP SPEAR T cells

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Background and aims: ADP-A2AFP specific peptide enhanced affinity receptor (SPEAR) T-cells are genetically engineered to target AFP+ tumors in the context of HLA-A*02, which are being evaluated in an ongoing Phase 1 trial in patients with hepatocellular carcinoma (HCC; NCT03132792). Here we describe late-breaking data from the 3rd dose cohort of this trial.

Method: First-in-human study in HCC, patients (pts) must be HLA-A*02:01$^+$ or 02:642$^+$ and have AFP expression by immunohistochemistry (IHC) at ≥1+ in ≥20% HCC cells or serum AFP ≥400 ng/ml (recently amended to ≥100 ng/ml), and ≤5% AFP expression by IHC in non-cancerous liver tissue. Up to 35 pts with HCC with modified 3+3 design. For Cohort 3, lymphodepletion is fludarabine 30 mg/m^2 QD for 4 days and cyclophosphamide 600 mg/m^2 QD for 3 days. Following lymphodepletion, target transduced cell dose for Cohort 3 was 5×10^9 (range: 1.2 to 6.0×10^9). Cohort expansion may occur allowing for doses up to 10×10^9 transduced cells.

Results: As of Feb 10, 2020, 3 pts (1 M, 2 F) were treated in Cohort 3 with 5.6, 5.0 and 5.1×10^9 transduced cells. Pts experienced cytopenias (up to G4 leukopenia, lymphopenia, and neutropenia) as well as febrile neutropenia related to lymphodepleting chemotherapy followed by recovery. There were no reports of T-cell related hepatic toxicity, although one pt had abnormal liver chemistries considered possibly related to ADP-A2AFP with evaluation ongoing. There have been no DLTs reported to date. High peak levels of peripheral SPEAR T-cells were observed up to 4 wks post-infusion.
The first pt in Cohort 3 had a confirmed partial response (cPR) with 100% reduction in target lesions; one non-target lesion remained at Wk 8. This was associated with rapid and sustained decrease in serum AFP levels from 6531 ng/mL at baseline to 14 ng/mL at Wk 12. The second pt had PD at Wk 4 with new liver lesions, and an increase in a single liver target lesion by 5% in SLD from baseline. This 2nd pt experienced a transient reduction from 2283 ng/mL at baseline to 1788 ng/mL at Wk 2 (22% reduction), with a subsequent increase to 2759 ng/mL at Wk 8. The third pt had PD at Wk 4 based on increased SLD from baseline. Serum AFP initially decreased at Wk 2 with a return toward baseline by Wk 4.

Conclusion: There have been no clear reports of T-cell related on-target or off-target toxicity, and no protocol-defined DLTs. There is promising early evidence of efficacy and these data support continued investigation.

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Late Breaker: Posters

LBP01

Multifactorial effects of AXA1125 and AXA1957 observed on markers of metabolism, inflammation and fibrosis: a 16-week randomized placebo-controlled study in subjects with non-alcoholic fatty liver disease (NAFLD) with and without type 2 diabetes (T2D)

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Background and aims: Effective and sustainable treatments for nonalcoholic steatohepatitis (NASH) will likely require simultaneously addressing metabolism, inflammation, and fibrogenesis. AXA1125 and AXA1957 are novel oral endogenous metabolic modulator (EMM) compositions of primarily amino acids. AXA1125-003 (NCT04073368) investigated the safety, tolerability, and physiologic effects of AXA1125 and AXA1957.
Methods: This multicenter, randomized, placebo (PBO)-controlled study enrolled 102 adult NAFLD subjects ±T2D, with proton density fat fraction (PDFF) ≥10% and corrected T1 [cT1] ≥830 msec by multiparametric MRI. Subjects received twice-daily administration of either AXA1125 24 g, AXA1957 13.5 g or 20.3 g, or PBO for 16 weeks. Safety and tolerability were assessed by laboratory measures and adverse events (AEs). Physiologic assessments included change from baseline in key markers of metabolism (MRI-PDFF and homeostasis model assessment of insulin resistance [HOMA-IR]) and fibroinflammation (alanine aminotransferase [ALT], cT1, cytokeratin-18 [CK-18], N-terminal type III collagen propeptide [pro-C3]). Here, we report interim analysis (IA) data for subjects who completed ≥ 1 postbaseline MRI.
Results: Baseline characteristics were suggestive of NASH (average MRI-PDFF >20%, cT1 >900 msec, FibroScan >10 kPa, and pro-C3 >16 ng/mL). Among 62 subjects evaluable for this IA, those receiving AXA1125 and AXA1957 showed improved MRI-PDFF, ALT, cT1, and CK-18 relative to PBO as early as Week 8 and sustained at Week 16. Roughly 50% and 30% of subjects receiving AXA1125 and AXA1957, respectively, had ≥30% relative reduction from baseline MRI-PDFF. Fifty percent of subjects dosed with either composition had ≥40 msec absolute reduction in cT1. AXA1125 treatment led to marked absolute reductions in HOMA-IR. Subjects showed improvements in ALT, especially in those with a decrease >17 IU/L. Differential changes in CK-18 and pro-C3 were noted. Both compositions were safe and well tolerated, with stable lipid profiles. Overall, product-related AE rates were low, mostly mild, with minimal discontinuation and no product-related serious AEs. Top-line results from the complete data set will be shown.
Conclusion: AXA1125 and AXA1957 were safe, well tolerated, and led to clinically relevant multifactorial effects. These EMM compositions represent a novel mode of action with the potential to simultaneously address NASH and key comorbidities, including insulin sensitivity.

LBP02

Lack of reliability of liver biopsies in non-alcoholic steatohepatitis (NASH) clinical trials - potential implications for developing new therapies for NASH

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Background and aims: Liver biopsies are a critical component of pivotal studies in nonalcoholic steatohepatitis (NASH) constituting main inclusion criteria, risk stratification factors and endpoints.
Method: We evaluated data from the EMMINENCE study examining a novel insulin sensitizer (MSDC-0602 K) in NASH. Digitized slides from 678 biopsies (baseline and 1 year follow up) for 339 patients were read independently by three hepatopathologists blinded to treatment code and scored using the NASH CRN Histological Scoring System. Inter-reader reliability was examined by comparing all possible pairs of the three hepatopathologists with respect to NASH CRN scores (ballooning, inflammation, steatosis, fibrosis); NAS, the sum of the ballooning, inflammation, and steatosis scores; and NASH diagnosis; as well as dichotomous derived endpoints at 12 months of NAS improvement with no concurrent worsening of fibrosis of ≥1 stage, and improvement of fibrosis by at ≥1 stage with no worsening of NASH. Reliability was assessed using unweighted and weighted kappa coefficients.
Results: Inter-reader linearly weighted kappas were 0.609, 0.484, 0.328, and 0.517 for steatosis, fibrosis, lobular inflammation, and ballooning, respectively. Inter-reader kappas were especially poor for the diagnosis of NASH (0.400), and also for the two currently approvable endpoints-NASH resolution without worsening of fibrosis (0.396), and fibrosis improvement without worsening of NASH (0.366) (Table).
Almost half of the patients enrolled were deemed not to have met the inclusion criteria by at least one hepatopathologist; all three hepatopathologists agreed that eligibility criteria were met for only 53.7% of these patients.
The average effect of MSDC-0602 K 125/250 mg combined versus placebo on 12-month changes in noninvasive markers of fibrosis and liver injury was almost double in terms of standard deviations (0.33 SDs) as compared to histologic endpoints (0.18 SDs), suggesting that the significant lack of reliability in hepatic histology interpretation may have reduced the apparent treatment effect of MSDC-0602 K. Indeed, the observed effect of MSDC-0602 K 125/250 mg combined versus placebo tended to be larger for NASH CRN features with higher reliability (r = −0.54).

Inter-reader reliability regarding endpoints derived from NASH CRN Scores for 339 patients with Paired Biopsies

Endpoint	Inter-reader Comparison	% Agreement*	% Agreement Expected by Chance*	Unweighted Kappa (95% CI)
Hepatic histological improvement in NAS	Original v. H1	71.68	54.62	0.376 (0.276, 0.476)
	Original v. H2	74.04	58.93	0.368 (0.264, 0.472)
	H1 v. H2	74.93	57.36	0.412 (0.310, 0.514)
	Average	73.55	57.17	0.382 (0.308, 0.456)
Resolution of NASH with no worsening of fibrosis	Original v. H1	79.65	60.09	0.490 (0.389, 0.590)
	Original v. H2	81.12	69.45	0.382 (0.268, 0.497)
	H1 v. H2	76.99	65.91	0.325 (0.219, 0.432)
	Average	79.25	65.65	0.396 (0.315, 0.477)
Improvement of fibrosis with no worsening of NASH	Original v. H1	76.11	60.70	0.392 (0.286, 0.497)
	Original v. H2	75.81	65.49	0.299 (0.184, 0.413)
	H1 v. H2	78.76	63.94	0.411 (0.301, 0.521)
	Average	76.89	63.53	0.366 (0.289, 0.444)
Resolution of NASH with at least a 2-point improvement in NAS	Original v. H1	80.53	67.11	0.408 (0.293, 0.523)
	Original v. H2	84.66	75.10	0.384 (0.256, 0.513)
	H1 v. H2	79.35	72.65	0.245 (0.125, 0.365)
	Average	81.51	71.87	0.343 (0.256, 0.430)
* Unevaluable score considered as a response category.				

Figure: (abstract: LBP02)

Simulations show that the lack of reliability in liver histology interpretations' effect on both eligibility ascertainment and assessment of treatment effect may reduce the power of a well-designed NASH study form > 90% to 40%.
Conclusion: Reliability of hepatopathologists' liver biopsy evaluation using currently accepted criteria is poor. This lack of reliability may affect NASH pivotal studies by introducing patients who do not meet NASH study entry criteria, misclassifying fibrosis subgroups, and attenuating apparent treatment effects.

LBP03

HM15211, a novel GLP-1/GIP/Glucagon triple-receptor co-agonist significantly reduces liver fat and body weight in obese subjects with non-alcoholic fatty liver disease: A Phase 1b/2a, multi-center, randomized, placebo-controlled trial

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Background and aims: NASH is a disease with a complex multifaceted pathophysiology. HM15211 is a novel long-acting GLP-1/GIP/Glucagon triple-receptor co-agonist, targeting NASH via multiple modes of action. HM15211 has shown therapeutic potential in animal models of obesity, NASH (AS015) and safe profiles in a previous first-in-human study (FRI115).
Method: Non-diabetic obese subjects with non-alcoholic fatty liver disease (NAFLD) were enrolled (MRI-PDFF ≥10%) in a Phase 1b/2a single-blind, randomized, placebo-controlled study to investigate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of multiple subcutaneous (SC) weekly doses of HM15211 for 12 weeks. In total 66 subjects were randomized, the baseline mean (SD) age of participants was 46 (11.4) years, 50.0% were women, BMI was 36 (4.96) kg/m^2 and liver fat by initial MRI-PDFF was 19.2 (6.5) %. The study was designed as a multiple ascending dose study, to test 5 different doses of HM15211 (0.01, 0.02, 0.04, 0.06, and 0.08 mg/kg), enrolling 12 subjects per cohort. Subjects were randomized to HM15211 or placebo in a ratio of 3:1 (9 on active, 3 on placebo). Week 12 MRI-PDFF data for final dosing (0.08 mg/kg) cohort will be presented at ILC.
Results: The mean (SD) relative changes from baseline in liver fat at week 8 were −14.9 (12.2) % for 0.01 mg/kg ($p = 0.13$), −43 (23.5) % for 0.02 mg/kg ($p < 0.0001$), −44.5 (46.6) for 0.04 mg/kg ($p = 0.0005$), −71 (23.8) % for 0.06 mg/kg ($p < 0.0001$), −80.3 (13.2) % for 0.08 mg/kg ($p < 0.0001$), vs. −1.2 (24.5) % for placebo group. The mean (SD) relative changes from baseline in liver fat at week 12 were −19.6 (12.2) % for 0.01 mg/kg ($p = 0.30$), −36 (28.1) % for 0.02 mg/kg ($p = 0.06$), −38 (53.5) % for 0.04 mg/kg ($p = 0.12$), −59.3 (27.6) % for 0.06 mg/kg ($p = 0.0020$), and −5.7 (37.8) % for placebo group. The liver fat reduction proportionally increased by escalating doses and the observed maximum liver fat reduction at week 12 was 88% by currently available data. HM15211 decreased body weight compared with placebo across all treatment groups. Placebo-corrected kg and % reduction of body weight were −1.3, −1.8*, −2.1*, −3.1*, and −4.3* kg (−1.2, −1.9*, −2.2*, −2.9*, and −4.4*%) at week 8 and −2.1, −3.1*, −1.9, −4*, and −5.3* kg (−1.9, −3.4*, −2.1, −3.8*, and −5.1* %) at week 12 in 0.01 to 0.08 mg/kg dose cohorts, respectively (*$p < 0.05$). HM15211 was shown to be well tolerated. The most common dose-dependent adverse events were mild gastrointestinal symptoms. Two subjects at different dosing cohorts developed hyperglycemia, but rapidly resolved with IP discontinuation. There were no deaths or serious adverse events related to HM15211 in any cohort.
Conclusion: HM15211 was safe and well tolerated during 12 weeks treatment in non-diabetic obese subjects with NAFLD.Treatment with HM15211 significantly decreased liver fat content and body weight in 8 and 12 weeks. Further development of HM15211 as a treatment for NASH is warranted.

LBP04

Liver toxicity in the Phase 2 Catalyst 206 trial of Inarigivir 400 mg daily added to a nucleoside in HBV EAg negative patients

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Background and aim: Inarigivir, an orally administered dinucleotide, activates RIG-I and has secondary *in vitro* properties of a non-nucleoside reverse transcriptase inhibitor of HBV. Over 250 pts with HBV or HCV have received inarigivir from 25 to 900 mg daily for between 1 to 12 wks, alone or in combination with a nucleoside analogue (NUC). The CATALYST Phase 2 trials were designed to assess longer treatment with inarigivir 400 mg daily in HBV pts, either alone or in combination with a NUC.

Methods: CATALYST 206 evaluated inarigivir 400 mg daily for 24 wks in NUC treated suppressed HBV pts; ARM 1 in pts who stopped their NUC and received inarigivir alone; ARM 2 added inarigivir to pts who continued NUC therapy. In December 2019, an unexpected series of mainly hepatic adverse events occurred in 7 pts treated in ARM 2 of CATALYST 206 resulting in immediate cessation of all inarigivir trials.

Results: 42 HBeAg-negative pts with normal ALT and HBV DNA <1.3 $\log_{10}$ in 7 sites in the UK and Canada were randomized to treatment with inarigivir 400 mg daily in ARM 2. There were 29 Asians, 8 African and 5 Caucasian pts; 27 male and 15 female, mean age 47.8 years (range 25–66 yrs). 7 pts presented with an SAE after a mean of 16 wks treatment (range 13–21 wks). All 7 had elevated ALT (maximal elevation mean 212 IU/L; range 116–412), 4 had associated hyperbilirubinemia >2 × ULN and 3 had abdominal pain. 1 pt was hospitalised with an ALT of 109 IU/L, bilirubin 68 umol/L and within 24 hours developed lactic acidosis, severe necrotizing pancreatitis with progressive liver failure and died from multi-organ failure. Another 6 pts developed elevated ALT >200 IU/L with no changes in bilirubin or synthetic function after stopping inarigivir while still on NUC. There was no obvious difference in age, gender, ethnicity or NUC therapy in those developing liver injury *vs* those who did not. PK trough levels for SB 9200 and its metabolites at wk 4 and 12 were no different between those with and without liver injury. 5 pts underwent liver biopsy but in only 1 was significant inflammation evident, predominantly findings of mild hepato-cellular injury and steatosis were seen, with significant cholestasis in 2 pts. Electron microscopy showed no significant ultra structural evidence of mitochondrial injury. In some pts, liver injury only occurred up to 3 wks after stopping inarigivir although a pattern of resolution was seen in all by 6 wks. Treatment with steroids, NAC and URSO was of questionable benefit. The efficacy endpoint of HBsAg reduction > 0.3$\log_{10}$ was seen in 23 pts (55%) with a mean reduction of 1.13$\log_{10}$ (range 0.5–2$\log_{10}$) and occurring between wks 6–12.

Conclusion: We describe an unusual, heterogeneous DILI observed after a mean of 16 weeks of inarigivir (400 mg daily) added to a NUC. Further studies are ongoing to identify causality and mechanisms. These findings have implications for trial design in HBV 'cure' studies and liver safety parameter monitoring.

LBP05

Antiviral activity, pharmacokinetics and safety of the second-generation hepatitis B core inhibitor ABI-H2158 in Phase 1b study of patients with HBeAg-positive chronic hepatitis B infection

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Background and aims: The HBV core protein plays an integral role in multiple steps of the HBV lifecycle. ABI-H2158 is a second-generation HBV core inhibitor in development for the treatment of chronic hepatitis B infection. Here we report the antiviral activity, pharmacokinetics (PK) and safety from a Phase 1b study in which patients (pts) were treated with ABI-H2158.

Method: In each cohort, 9 pts (7 active, 2 placebo [Pbo]) were randomized in a blinded manner to receive either ABI-H2158 100, 300 or 500 mg or Pbo once daily for 14 days. Eligible pts were males or females aged ≥18 and ≤65 years, HBV treatment naive, HBeAg positive with HBV DNA ≥2×10^5 IU/mL and Metavir F0-F2. HBV DNA, pgRNA, HBeAg, HBsAg and HBcrAg were measured on Days 1, 8 and 15. PK was assessed on Days 1 and 14. Safety was evaluated by treatment-emergent adverse events (AEs) and laboratory parameters.

Results: Across the cohorts, the mean (range) age of pts was 36 (19–51) years, with the majority being male (59%), Asian (96%) and HBV genotype C (59%). At baseline, the mean (range) HBV DNA was 8.0 $\log_{10}$ (4.7–9.1) IU/mL, pgRNA was 6.8 $\log_{10}$ (5.2–7.9) U/mL and ALT was 40 (14–124) U/L. Change in HBV DNA and pgRNA from baseline to Day 15 and PK data are shown in the Table 1. AEs were reported for 38% (8/21) of pts receiving ABI-H2158 and 50% (3/6) receiving PBO. The majority of AEs were Grade 1; none were Grade 3 or 4, serious or led to treatment discontinuation. Headache was the only AE reported by more than 1 pt receiving ABI-H2158 (2 pts). Graded laboratory abnormalities were observed in 71% (15/21) of pts receiving ABI-H2158 and 50% (3/6) receiving Pbo, the majority of which were Grade 1. Transient increases in ALT were observed in 24% (5/21) of pts receiving ABI-H2158 (all Grade 1) and in 33% (2/6) receiving Pbo (1 Grade 1; 1 Grade 3).

	ABI-H2158			
	100 mg (n = 7)	300 mg (n = 7)	500 mg (n = 7)	Placebo (n = 6)
HBV DNA change from Baseline ($\log_{10}$ IU/mL), mean (range)	−2.3 (−3.0 to −1.7)	−2.5 (−3.3 to −0.8)	−2.7 (−3.2 to −1.7)	−0.1 (−0.3 to 0.1)
pgRNA change from Baseline ($\log_{10}$ U/mL), mean (range)	−2.1 (−2.7 to −1.5)	−2.2 (−2.6 to −1.4)	−2.0 (−3.5 to −1.3)[a]	−0.1 (−0.2 to −0.1)
C_{max}, ng/mL	3,390	8,400	9,890[a]	–
AUC_{0-24}, hr*ng/mL	46,100	112,000	133,000[a]	–

[a]n = 6.

Conclusion: Results from this Phase 1b study demonstrate that ABI-H2158 has potent antiviral activity and a favourable safety profile when administered once daily for 14 days supporting further evaluation in combination with nucleos(t)ide analogues in Phase 2.

LBP06

Wide variations in liver transplantation (LT) policies across Europe for patients with acute-on-chronic liver failure (ACLF) despite excellent post-LT survival: Results of a CLIF/ELITA collaborative study

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Background and aims: 28-day mortality of ACLF patients increases with its severity. LT has been shown to be an effective salvage therapy even for the sickest patients with ACLF, but most of the data are derived from retrospective single centre studies or from registries, which fail to provide granular information. The attitudes, clinical approach, outcomes of wait listed (WL) and LT patients in Europe is unknown. This study was designed to address these questions as a part of a collaboration between ELITA and EF-CLIF.
Method: 20 Centres from 8 European countries were involved. 2607 consecutive patients undergoing LT between January 2018 to June 2019 and 75 patients listed for ACLF, but dying on the waiting list during the same time frame were the subjects of this study. 223 ACLF patients on ICU but not wait-listed served as disease controls.
Results: Of these 2607 patients, 1188 (45.6%) received a LT for decompensated cirrhosis, 863 (33.1%) for HCC and 556 (21.3%) for other reasons. Of the 1188 LT candidates with decompensated cirrhosis, 228 (19.1%) had ACLF at LT; ACLF1: 57 (4.8%), ACLF2: 76 (6.4%) and ACLF3: 95 (8%). Wide variations were observed among countries, with France and Germany having high rates of ACLF2-3 at LT (25–40%); Italy, Switzerland, Poland and Netherlands medium rates (7–14%) and UK and Spain low rates (3–5%) ($p < 0.0001$). Patients with ACLF2-3 received an LT after a median of 6-days compared with ACLF1 patients who received an organ after 17-days ($p < 0.0001$). Overall 1-year survival after LT was 81% (95%CI: 74–87), independent of the ACLF grade (FIG). Bacterial infection (59%) and alcoholic hepatitis (19%) were the most prevalent precipitating factors. Pre LT arterial lactate levels higher than 4 (HR 3.49; 95% CI 1.12–10.85) and recent infection from multi-drug resistant organisms (HR 3.2; 95% CI 1.07–9.75) were independent predictors of post-LT mortality. When including in the analyses the 75 patients that were listed for ACLF, but died on the WL, the 1-yr survival from listing was only 51% (95%CI: 41–59) in those with ACLF3 with 36% dying on the WL (FIG). Mortality of contemporaneous controls not listed for LT was commensurate with expected high mortality.
Conclusion: The results reveal wide variations in attitudes to listing and transplanting patients with ACLF in Europe despite clear evidence of excellent post-LT survival and transplant benefit

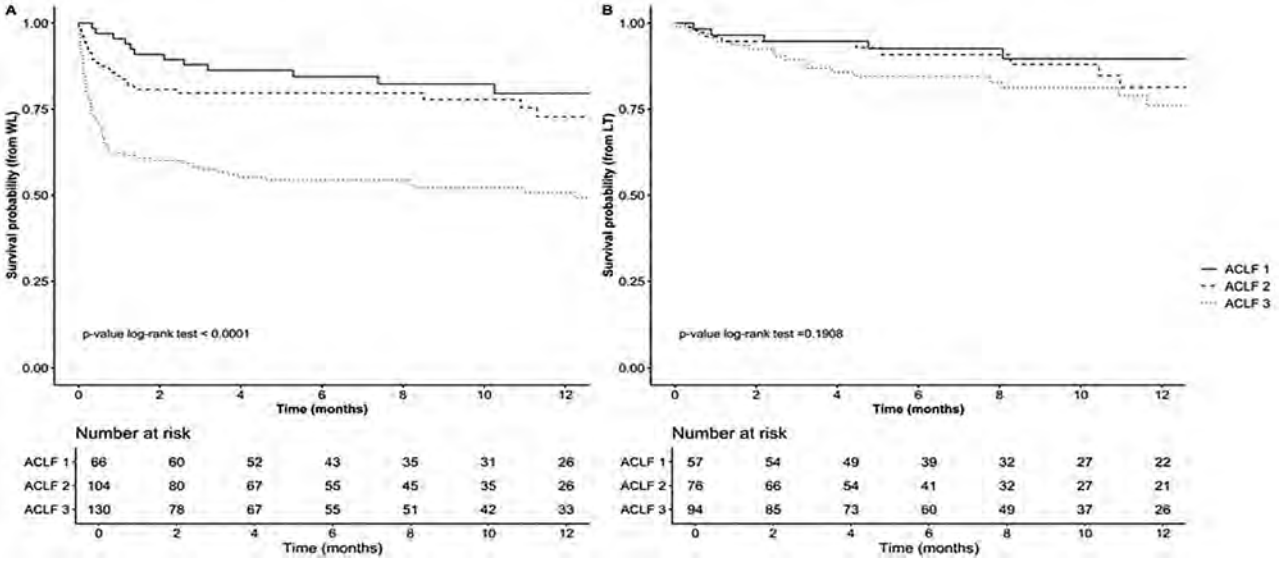

Figure: (abstract: LBP06): Survival after WL (panel A) and after LT (panel B).

emphasizing the need for harmonisation. The current allocation policies do not address the urgency for ACLF patients suggesting need for changing allocation policies.

LBP07

Declining HCV incidence following rapid HCV treatment scale-up in a prison network in Australia: Evidence of treatment as prevention from the SToP-C study

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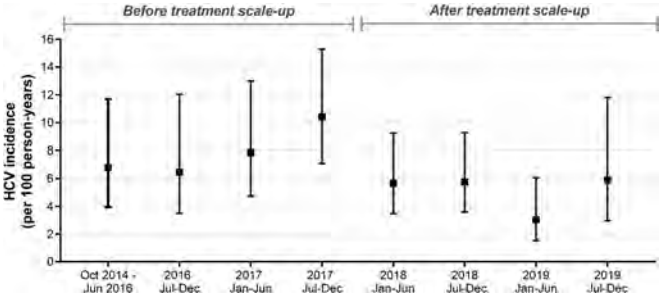
Background and aims: There are no large scale interventional trials supporting HCV treatment as prevention (TasP). The Surveillance and Treatment of Prisoners with hepatitis C (SToP-C) study assessed HCV TasP in four Australian prisons.

Method: SToP-C enrolled people incarcerated in two maximum (male) and two medium security prisons (one male, one female) where opioid agonist therapy (OAT) but not needle-syringe programs were available. Following HCV antibody (Ab) and RNA screening, participants were monitored six monthly for risk behaviors and HCV, with three sub-populations: (1) uninfected (Ab–); (2) previously infected (Ab+/RNA–); (3) infected (Ab+/RNA+). Uninfected and previously infected (at-risk) participants were followed for HCV primary and reinfection, while infected participants were assessed for treatment. Enrolment commenced October 2014 with final follow-up November 2019. HCV treatment was provided to small numbers by prison health service until mid-2017, when intensive DAA scale-up (12 weeks sofosbuvir/velpatasvir) through SToP-C was introduced. HCV incidence was compared between before and after treatment scale-up periods.

Results: Of 3,640 participants enrolled, 710 (19%) had detectable HCV RNA and 2,930 were at-risk of primary infection (n = 2,217) or reinfection (n = 713) at baseline. Enrollment coverage was 53–89% across prisons. DAA treatment was initiated in 324/397 (81%) RNA+ participants during scale-up period. The at-risk population with longitudinal follow-up (n = 1,637) had median age 33 years; and included 82% male; 47% history of injecting drug use (of whom 28% received OAT). Among at-risk population, 56/1,066 primary infection and 56/571 reinfection events were detected. During 1,764 person-years (py) follow-up, HCV incidence was 6.4/100 py (95%CI: 5.3, 7.7): primary infection 4.6/100 py (3.5, 5.9), and reinfection 10.6/100 py (8.2, 13.8). HCV incidence declined from 8.1/100 py (6.4, 10.4) prior to treatment scale-up to 5.0/100 py (3.8, 6.6) following (p = 0.032; Figure), including 49% reduction in primary infection from 6.5/100 py (4.7, 9.0) to 2.9/100 py (1.9, 4.6; p = 0.018), and non-significant 20% reduction in reinfection from 12.3/100 py (8.4, 17.9) to 9.4/100 py (6.5, 13.5; p = 0.42).

Conclusion: Rapid scale-up of DAA therapy was associated with HCV incidence reduction in prison, indicative of TasP. The findings support broad DAA scale-up among incarcerated populations, and enhanced harm reduction in this population, particularly for prevention of reinfection.



LBP08

faecal microbiota transplantation reduces pathogenic burden and is anti-inflammatory in patients with advanced cirrhosis

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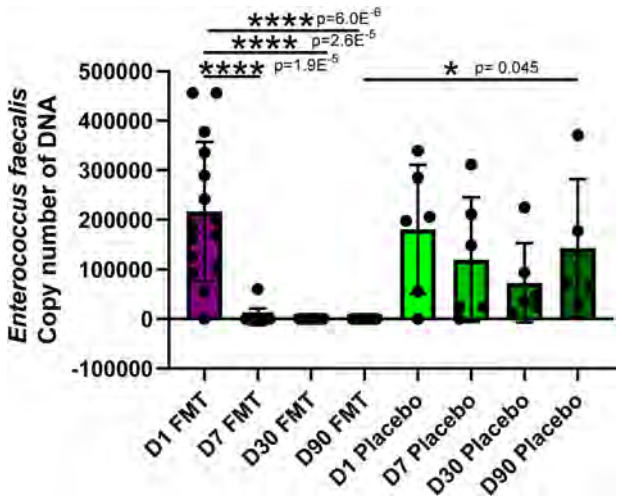
Background and aims: Patients with advanced cirrhosis have enteric dysbiosis with small bowel bacterial overgrowth and translocation of bacteria and their products across the gut epithelial barrier. This culminates in systemic inflammation and endotoxaemia, inducing innate immune dysfunction, which predisposes to infection, and multi-organ dysfunction. We hypothesised that modifying the gut microbiota with Faecal Microbiota Transplantation (FMT) may reduce the progression of chronic liver failure.

Method: The prospective, randomised, single-blinded, feasibility trial evaluating FMT (n = 15) against placebo (n = 6) [PROFIT Trial NCT02862249] was completed in late 2019. Patients were evaluated then administered FMT/placebo into the jejunum within 7 days of baseline. To assess the stability of transplanted gut microbiome and its efficacy in modulating the patient's own microbiome, disease and inflammatory status: urine, blood, saliva and stool were collected at days 0, 7, 30 and 90 post-FMT administration. To compare the composition of the faecal and oral microbiota with the donor microbiome, DNA was extracted from matched stool and saliva samples for metagenomic analyses and for qPCR of selected enteropathogens. Serum samples were analysed for immune function assays e.g. Tru-culture to assess the cytokine production after whole blood stimulation with stimulants such as LPS, heat-killed *E. coli* in comparison to null samples.

Results: FMT was associated with a reduction by day-90 in stool *Enterococcus faecalis* (p = 0.000006, Figure 1) and enteropathogenic (EPEC) *Escherichia coli* (p = 0.0033), but not in the placebo group. EPEC causes barrier damage and *E. faecalis* hydrolyses arginine to produce ammonia and produces a pore-forming toxin cytolysin that causes barrier damage. FMT eradicates cytolysin and reduces systemic inflammation with an increase in the production of the anti-inflammatory cytokines IL-10 and IP-10 at day-7 (p = 0.004 and p = 0.0002, respectively). TNFα is enhanced in the FMT group at day 7 (p = 0.0025) and maintained up to day 90. The antibacterial properties of TNFα may account for the loss of pathogenic bacterial species.



Conclusion: FMT reduces the pathogenic bacterial burden, removing enteric pathogens known to cause epithelial gut barrier disruption and modifies the systemic inflammatory profile in patients with cirrhosis. It may be possible to alter the microbiota to promote barrier repair and to restore immune tolerance in cirrhosis.

LBP09

The impact on mortality of a national hepatitis C elimination program, Georgia, 2015–2019

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Background and aims: Georgia embarked on a national hepatitis C elimination program in April, 2015, which provided direct acting antiviral (DAA) medications free of charge to all hepatitis C virus (HCV) infected persons. We aimed to evaluate the impact of the program on all-cause mortality.

Method: We identified adults (≥18 years) registered in the national hepatitis C screening registry from April 2015 through May 2018 and linked these data to the national hepatitis C treatment database and national vital statistics using the 11-digit national personal identifier. We used vital statistics data to identify deaths through December 2018. Kaplan-Meier survival plots were generated to determine and compare survival among three groups: HCV-uninfected persons (screened negative for anti-HCV), persons HCV-infected (confirmed by viremia testing) who were not treated, and persons with HCV infection confirmed by viremia testing who were treated and cured (i.e. achieved sustained virologic response; SVR). We calculated adjusted hazard ratios (aHR) using Cox proportional hazards regression models for the three groups after controlling for sex, age, and hospitalization-regardless of the admission diagnosis.

Results: We identified 1,002,229 HCV-uninfected persons, 14,234 HCV-infected persons who were not treated, and 32,485 patients who were HCV infected and cured of their infection (achieved SVR). Untreated HCV-infected persons as well as those who were infected and achieved SVR were mostly men (73.4% and 79.8% respectively), while 57.7% of uninfected persons were females. Uninfected persons were slightly younger than those infected and not treated, and those who were cured (median ages: 43, 49 and 45, respectively) ($p < 0.0001$). The Kaplan-Meier analysis revealed that a greater proportion of untreated HCV-infected persons died during the study period compared to both uninfected and HCV cured persons (Figure). Overall, untreated persons had the highest proportion of deaths (8.0%; n = 1140), followed by uninfected (4.4%; n = 44, 047) and cured persons (1.8%; n = 575). In adjusted models, untreated HCV-infected persons were more likely to die compared with uninfected persons (aHR 2.34; 95%CI 2.20–2.48) and those who achieved SVR (aHR 3.12; 95%CI 2.82–3.45).

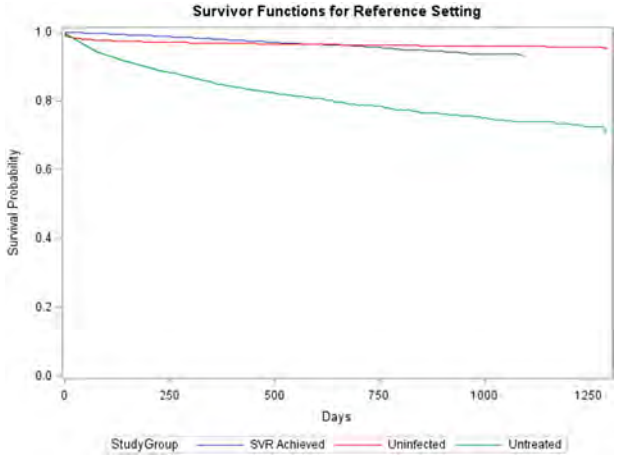

Figure: Comparison of Kaplan-Meier survival curves between study groups, adjusted for sex, age and hospitalization events.

Conclusion: Our findings demonstrate that persons with HCV infection who are cured with DAAs have an increased likelihood of survival, similar to persons never infected, when compared to HCV-infected persons who did not receive treatment.

LBP10

Bariatric surgery is not associated with a reduction in risk of severe liver disease in comparison to standard obesity treatment in 3,922 subjects

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Background and aims: Bariatric surgery is associated with a reduced overall mortality as well as improvement in histological features of non-alcoholic fatty liver disease (NAFLD). However, it is unclear if this translates to a reduced incidence of clinically relevant outcomes such as hepatocellular carcinoma (HCC) or decompensated cirrhosis.

Method: We used data from the Swedish Obese Subjects study, a matched controlled study comparing bariatric surgery (n = 2010) and conservative obesity treatment (n = 2037) with recruitment between 1987–2001. We excluded participants with any pre-existing liver disease except NAFLD at baseline (n = 125). The main outcome was a composite endpoint of ICD-based diagnoses including cirrhosis, decompensation events, HCC or death in liver disease, ascertained by linkage to Swedish national registers until the end of 2016. Patients were classified as having alcohol-related cirrhosis if there were any ICD-coding for alcohol use disorder or alcohol-related liver disease during follow-up. Cox regression was used to estimate hazard ratios

for severe liver disease, after adjustment for age, sex and baseline AST/ALT ratio.

Results: At baseline, mean age in the surgery group was 47.1 years, and 28.3% were males. Mean BMI was 42.4 kg/m^2, and 17.1% had type 2 diabetes. During a median follow-up of 21 years (interquartile range 17–24), there were 47 cases (2.2%) of severe liver disease in the surgery group, and 44 (2.3%) in the control group (p = 0.48). We found no increased risk of severe liver disease in the surgery group compared to the conservative obesity treatment group in the regression analysis (aHR = 0.94, 95%CI = 0.62–1.42, figure 1). Results were consistent across pre-defined sensitivity analyses. There was a non-significant trend of increased risk of alcohol-related cirrhosis in the surgery group (aHR 1.88, 95%CI = 0.75–4.73), but reduced risk for non-alcoholic cirrhosis (aHR 0.68, 95%CI = 0.42–1.09).

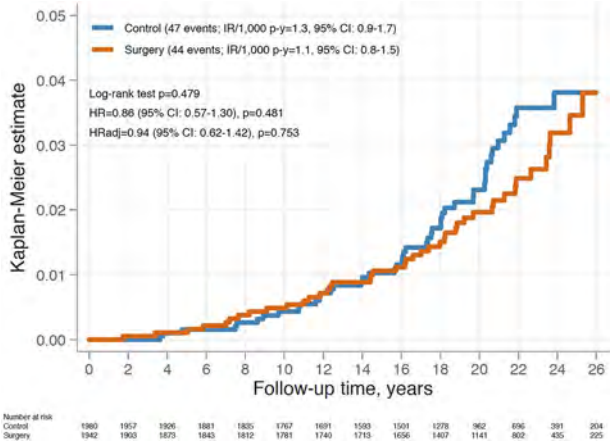

Figure 1. Kaplan-Meier failure curve of severe liver disease in surgery and control groups.

Conclusion: We found no association between bariatric surgery and reduced incidence of severe liver disease over long term in comparison to standard obesity care in this study. The result may, however, be a sum of a dual effect of an increased risk for alcohol-related cirrhosis but a reduced risk of cirrhosis attributed to NAFLD in the surgery group.

LBP12

Efficacy and safety results of the phase 2 JNJ-56136379 JADE study in patients with chronic hepatitis B: Interim week 24 data

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Background and aims: JNJ-56136379 (JNJ-6379) is a potent capsid assembly modulator producing normal empty capsids (CAM-N). We present wk 24 efficacy and safety from the ongoing Ph2 JADE study (NCT03361956) in chronic hepatitis (CHB) patients (pts).

Method: CHB not treated at study start (NT) and virologically suppressed (VS) HBeAg+ or HBeAg– pts were randomized to 75/250 mg JNJ-6379 qd or placebo (pbo) with a nucleos(t)ide analogue (NA; TDF/ETV) or received JNJ-6379 alone. As JNJ-6379 monotherapy will not be developed further, data from the combination arms are presented here. Primary endpoint was change from baseline (BL) in HBsAg at wk 24.

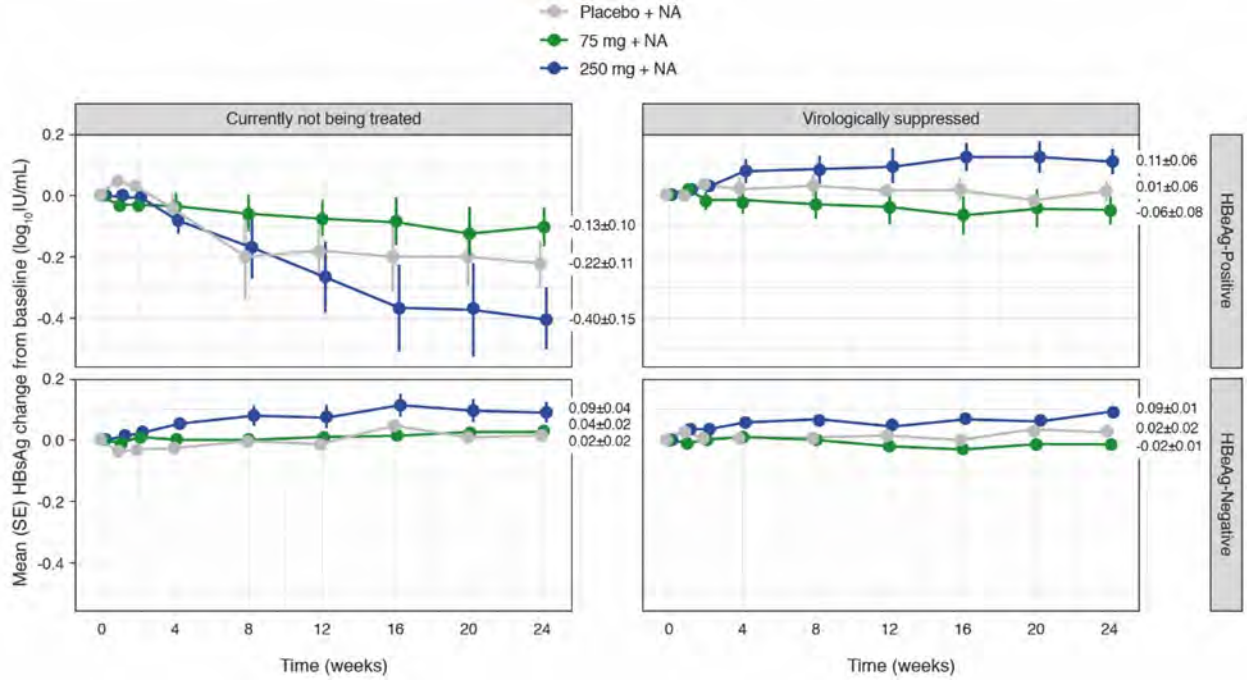

Figure: (abstract: LBP12): Mean (SE) change in HBsAg over 24 wks of treatment from baseline by population.

Results: Of 172 pts in the combination arms (88 NT; 84 VS), 48% were Asian and 34% HBeAg+.
In NT HBeAg+ pts, a more pronounced mean (SE) DNA decline from BL at wk 24 was observed for JNJ-6379 75 mg and 250 mg + NA [5.53 (0.23) and 5.88 (0.34) log_{10} IU/mL] over NA+pbo [5.21 (0.42)]; HBV DNA was <LLOQ in 0/12, 4/11 (36%) and 1/8 (13%) pts, respectively.
At wk 24 in NT HBeAg±pts, JNJ-6379 75 mg and 250 mg + NA showed an increased mean (SE) HBV RNA decline from BL [2.82 (0.25) and 3.13 (0.35) cp/mL] over NA+pbo [1.43 (0.32)]. HBV RNA was target not detected (TND) at wk 24 in 16/27 (59%), 19/25 (76%) and 9/20 (45%) NT HBeAg+/– pts, respectively. All JNJ-6379 VS pts with detectable HBV RNA at BL achieved HBV RNA TND at wk 24 vs 0% with NA+pbo.
JNJ-6379 250 mg+NA showed a mean (SE) HBsAg decline of 0.40 (0.15) log_{10} IU/mL in NT HBeAg+ pts at wk 24 (Figure). Pts with HBsAg decline also had HBeAg and HBcrAg declines and frequently early on treatment isolated ALT flares.
Maximal JNJ-6379+NA individual HBsAg and HBeAg reductions were 1.28 and 1.8 log_{10} IU/mL, respectively. Proportions of JNJ-6379+NA NT HBeAg+ pts with >0.3 log_{10} IU/mL reductions from BL in HBsAg and HBeAg were 8/23 (35%) and 19/23 (83%) vs 1/8 (13%) and 4/8 (50%) NA +pbo, respectively. Proportions of VS JNJ-6379+NA HBeAg+ pts with >0.3 log_{10} IU/mL reductions in HBeAg were 6/19 (32%) vs 1/5 (20%) NA +pbo.
No study treatment related serious adverse events or clinically significant changes in laboratory parameters occurred.
Conclusion: In not treated pts, JNJ-6379+NA increased HBV DNA suppression over NA alone. A mean 0.4 log_{10} IU/mL HBsAg decline with JNJ-6379 250 mg+NA was seen in NT HBeAg+ pts. JNJ-6379+NA was safe and well tolerated, supporting evaluation of JNJ-6379 in combination with an NA and the siRNA JNJ-73763989 in the ongoing Ph2 REEF-1 study (NCT03982186).

LBP13

A Phase 2 Study of Peginterferon Lambda, Lonafarnib and Ritonavir for 24 Weeks: End-of-Treatment Results from the LIFT HDV Study

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Email: christopher.koh@nih.gov.

Background and aims: Hepatitis Delta Virus (HDV) infection, the most aggressive form of human chronic viral hepatitis, is still without an approved FDA therapy. Clinical trials have demonstrated anti-HDV activity with the prenylation inhibitor lonafarnib (LNF) boosted with ritonavir (RTV) and peginterferon lambda-1a (LMD) monotherapy. In a first-in-humans clinical trial, the Lambda InterFeron combination Therapy (LIFT) study evaluated the safety and antiviral effects of combination therapy with LMD/LNF/RTV in patients with chronic HDV infection.
Method: In this phase 2a open-label study, 26 adult patients with chronic HDV and quantifiable HDV RNA in serum (lower limit of quantitation <40 IU/mL) have completed treatment with subcutaneous LMD 180 mcg weekly and oral LNF 50 mg and RTV 100 mg twice daily for 24 weeks and are undergoing per-protocol post-therapy monitoring for 24 weeks. Tenofovir or Entecavir was started prior to therapy. Serial assessments of safety parameters, liver tests, pharmacokinetics, histology, and virologic (HDV RNA and HBV DNA) markers were obtained.
Results: In this ongoing study, patients were 62% male, median age of 40 years and included Asian (54%), White (31%) and African (15%) subjects. Median baseline evaluations included: ALT (62 IU/mL), AST (47 IU/mL), Ishak Fibrosis (3), modified HAI inflammation (9), HBV DNA (<21 IU/mL) and log HDV RNA (4.7 IU/mL). After 12 weeks of therapy, the median HDV RNA decline from baseline was 3.4 log IU/mL (IQR: 2.9–3.8, $p < 0.0001$) with 7 patients (27%) achieving undetectable HDV RNA and 6 patients (23%) with HDV RNA below the lower limit of quantification (BLOQ). At the end of therapy, the median HDV RNA decline was 3.4 log IU/mL (IQR: 2.9–4.5, $p < 0.0001$) with 11 patients (42%) achieving undetectable HDV RNA and 3 patients (11%) BLOQ. 25 of 26 patients (96%) achieved >2 log decline during 24 weeks of therapy. Adverse events were mostly mild to moderate and included GI related side effects, weight loss, hyperbilirubinemia, and anemia. Therapy was dose reduced in 3 patients and discontinued in 4 patients.
Conclusion: Triple combination therapy with LMD/LNF/RTV in chronic HDV patients appears to be safe and tolerable for up to 6 months in most patients. After 24 weeks, almost all achieve >2 log decline in HDV RNA during therapy with >50% achieving undetectable or BLOQ HDV RNA levels. These end-of-treatment results support continued exploration of this therapeutic combination in HDV.

LBP14

Proof-of-concept use of machine learning to predict tumor recurrence of early-stage hepatocellular carcinoma before therapy using baseline magnetic resonance imaging

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Background and aims: Patients with early-stage hepatocellular carcinoma (HCC) are likely to experience tumor recurrence after initial therapy using thermal ablation, surgical resection or orthotopic liver transplantation (OLT), with some reports demonstrating recurrence rates up to 80% five years post-treatment depending on therapy option. Successful identification of patients who will likely recur could help optimize follow-up imaging, influence choice of adjuvant therapy, and could even improve transplant allocation. Currently, no biomarkers exist that can reliably predict recurrence. The combination of computational power and advanced machine learning-based algorithms allow in-depth exploration of imaging data to discover features predictive of recurrence. This study analyzed baseline magnetic resonance imaging (MRI) using state-of-the-art machine learning algorithms to predict HCC recurrence after first-line therapy with thermal ablation, surgical resection or OLT.
Method: This was a HIPAA-compliant, IRB-approved retrospective study with 120 patients who underwent either thermal ablation, surgical resection or OLT as first-line, stand-alone treatment for HCC between 2005 and 2018. Multiparametric contrast-enhanced MRI was analyzed by our machine learning model, which combined two readily available algorithms: VGG16 and XGBoost. The imaging dataset was labelled in six categories, with time-to-recurrence cutoffs at 1, 2, 3, 4, 5, or 6 years. Area under the receiver operating characteristic curves (AUC-ROC) was used to evaluate algorithm performance. Recurrence-free survival (RFS) was evaluated by Kaplan-Meier analysis, and survival curves were compared using the log-rank test.
Results: Of the 120 patients, 44 (36.7%) recurred at the time of analysis. Surgical resection (n = 32, 26.7%), thermal ablation (n = 29, 24.2%), and OLT (n = 59, 49.1%) were the treatment modalities. With 1, 2, 3, 4, 5 and 6 years as the time-to-recurrence cutoff, AUC-ROC values

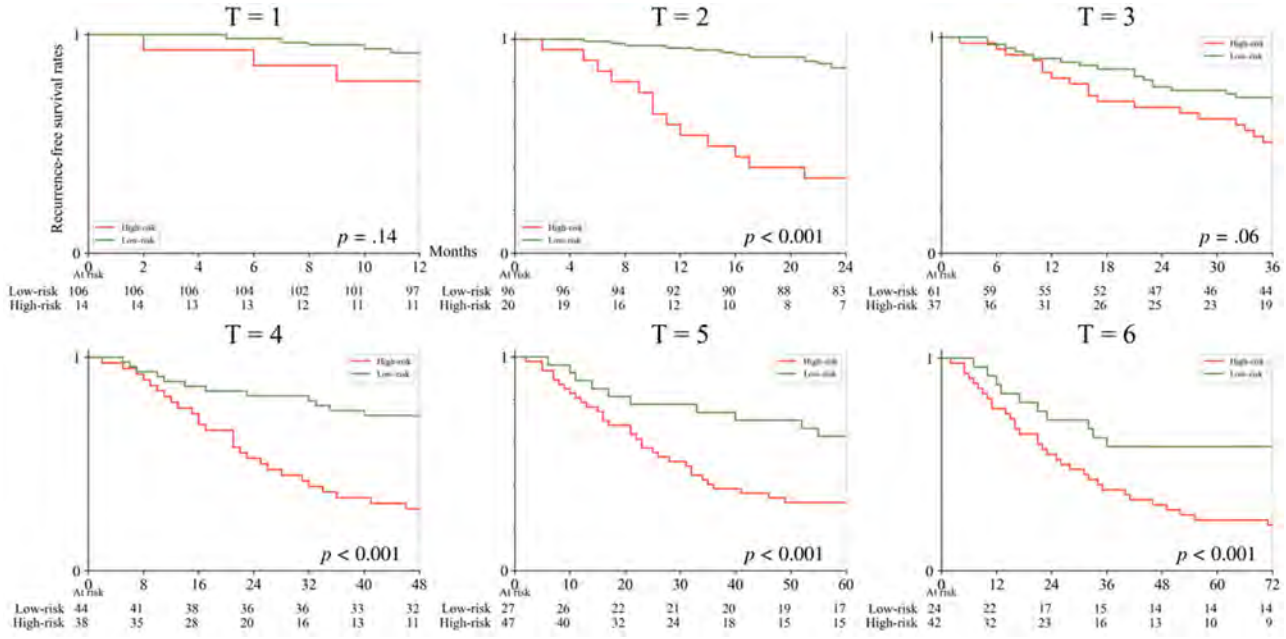

Figure: (abstract: LBP14): Kaplan-Meier analysis of Recurrence-free-survival (RFS) at each time-to-recurrence cutoff timepoints according to algorithm predictions. Each event on the green curve represents prediction inaccuracy (false-negative) and each event on the red curve represents an accurate prediction of recurrence (positive predictive value).

were, 0.74, 0.73, 0.71, 0.82, 0.71 and 0.79, respectively. Our algorithm was able to predict RFS with statistical significance at the 2, 4, 5, and 6-year time-to-recurrence cutoffs based on Kaplan-Meier analysis (log-rank p < 0.001).

Conclusion: Our study shows that machine learning-based algorithms can predict tumor recurrence of early-stage HCC prior to therapy using baseline MRI. Future developments could improve model sensitivity using larger (and external) patient cohorts and including clinical variables.

LBP15

Hepatocyte-specific deficiency of sphingosine kinase 1 exacerbates acetaminophen-induced liver injury

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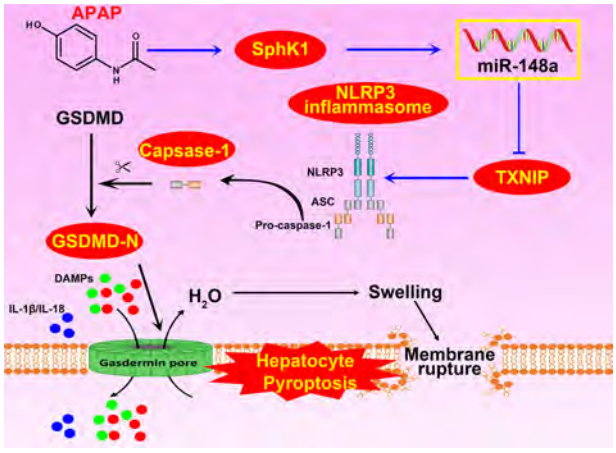
Background and aims: Sphingosine kinase 1 (SphK1) plays crucial roles in liver injury. Whether hepatocyte pyroptosis participates in the early stage of acetaminophen (APAP)-induced liver injury are not well understood. This study aims to investigate the role of hepatocellular SphK1 in APAP-induced hepatocyte pyroptosis and acute liver injury.

Method: Liver tissues from patients with DILI (DILI, n = 9) was obtained to examine the expression of SphK1. Hepatocyte-specific SphK1 conditional knockout (SphK1Hep−/−) and wild type (WT) mice (n = 6 for each group) were administrated with 250 mg/kg of APAP. Primary mouse hepatocytes isolated from WT and SphK1Hep −/− mice were treated with 5 mM APAP.

Results: SphK1 was strongly induced in patient and WT mice exposed to excess APAP. Surprisingly, SphK1Hep−/− mice had significantly higher mortality and elevated early hepatotoxicity compared to WT mice after APAP treatment. Conditional deletion of hepatocellular SphK1 increased hepatocyte pyroptosis and death. The enhanced hepatotoxicity in SphK1Hep−/− mice was associated with increased activation of NLRP3 inflammasome and Caspase 1 maturation and membrane rupture. Moreover, SphK1 deficiency in hepatocytes upregulated thioredoxin interacting protein (TXNIP) and downregulated miR-148a-3p. Furthermore, miR-148a-3p directly inhibited TXNIP expression. In contrast, APAP-induced NLRP3 activation and hepatocyte pyroptosis were reversed by miR-148a-3p mimic or TXNIP siRNA. Finally, the protective roles of SphK1 in hepatocyte damage was further strengthened by the results of adenovirus-mediated SphK1 overexpression in APAP-induced mice and correlation analysis of patients with AILI.



Conclusion: These data highlight a novel mechanism that the early stage of APAP-induced liver injury is characterized by hepatocyte pyroptosis, and demonstrate for the first time a protective role of hepatocellular SphK1 expression after APAP overdose via inhibition of NLRP3 inflammasome and pyroptosis.

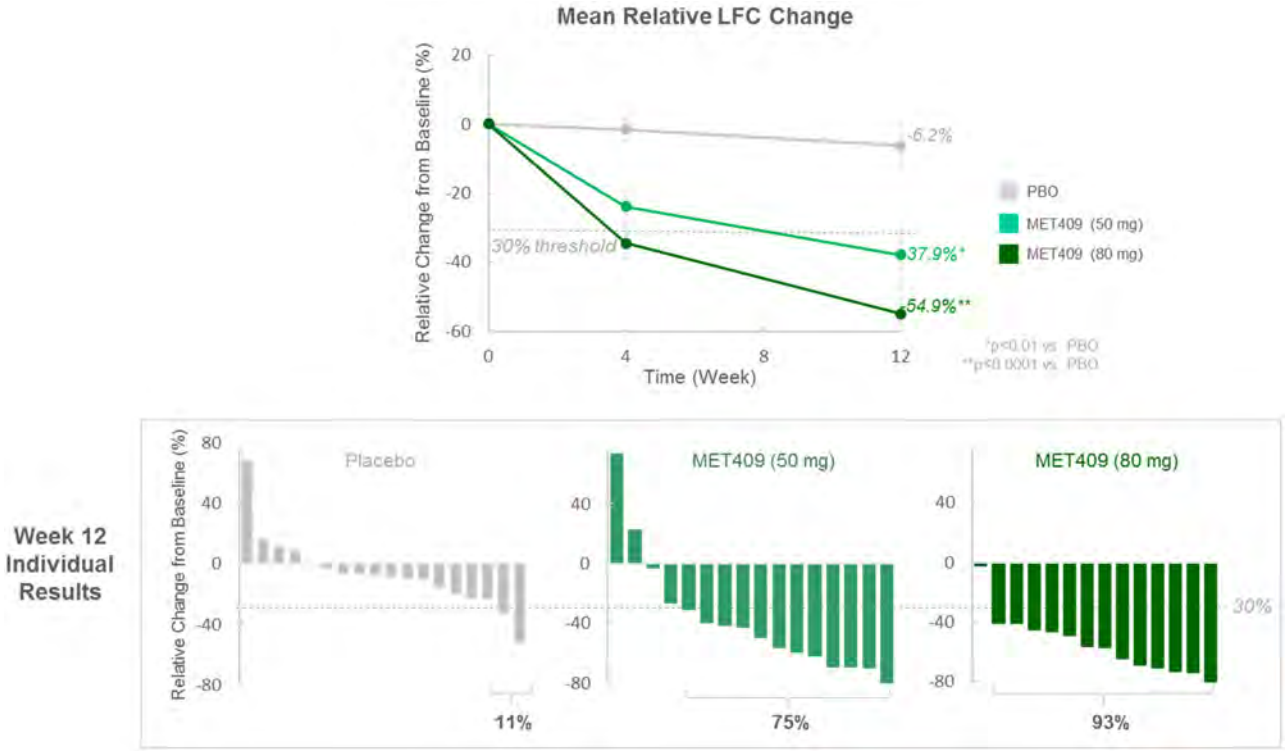


Figure: (abstract: **LBP16**)

LBP16

MET409, an optimized farnesoid X receptor agonist, decreased liver fat and improved liver enzymes in patients with non-alcoholic steatohepatitis: a 12-week, randomized, placebo-controlled study

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Background and aims: Farnesoid X receptor (FXR) agonists have been validated to benefit patients with non-alcoholic steatohepatitis (NASH), although improvements in therapeutic index for the class remain elusive. MET409, a sustained agonist with a novel non-bile acid structure, demonstrated an encouraging profile after 14 days of dosing in healthy subjects and 28 days of dosing in an open-label study in 10 NASH patients. We now report the results of a 12-week, randomized, placebo (PBO)-controlled study.
Method: Men and women (18–75 years-old) with biopsy-confirmed NASH or liver stiffness ≥8.5 kPa on transient elastography (TE) were eligible. All subjects had ≥10% liver fat content (LFC) by magnetic resonance imaging-proton density fat fraction. Three cohorts were enrolled: 80 mg (n = 20), 50 mg (n = 19), and PBO (n = 19).
Results: At Week 12, MET409 significantly lowered LFC, with mean relative reductions of 55% (80 mg) and 38% (50 mg) vs 6% in PBO. MET409 achieved ≥30% relative LFC reduction in 93% (80 mg) and 75% (50 mg) of patients vs 11% in PBO, and normalized absolute LFC (≤5%) in 29% (80 mg) and 31% (50 mg) of patients vs 0% in PBO. MET409 resulted in ≥30% relative alanine aminotransferase (ALT) reduction in 50% (80 mg) and 31% (50 mg) of patients vs 17% in PBO, and ≥30% relative gamma-glutamyl transferase reduction in 64% (80 mg) and 81% (50 mg) of patients vs 0% in PBO. Despite a transient ALT increase in a subset of MET409 patients at both dose levels, a mean decrease (−24.9%) was seen for 80 mg at Week 12. Pruritus (mild-moderate only) was reported by 10% (50 mg) and 35% (80 mg) of patients. Only two pruritus-related early terminations occurred, both at 80 mg (10%). On-target increases in low-density lipoprotein cholesterol (LDL-C) were seen with MET409 (mean change; 80 mg: +23.7%, 50 mg: +7.8%, PBO: −1.5%). MET409 led to a slight body weight loss (mean change; 80 mg and 50 mg: −2.7 kg, PBO: −0.5 kg). There were no treatment-related serious or severe adverse events.
Conclusion: MET409 significantly decreased LFC and improved liver enzymes after 12 weeks of treatment in patients with biopsy-confirmed or phenotypic NASH based on TE. Additionally, MET409 at 50 mg delivered a differentiated, favorable pruritus and LDL-C profile. These results provide the first clinical evidence that the therapeutic index of FXR agonists can be enhanced through structural optimization. Further development of MET409 and structurally-related agonists should be evaluated.

LBP17

BMS-986263 (novel targeted lipid nanoparticle delivering HSP47 siRNA) safety and target engagement in patients with advanced hepatic fibrosis: week 36 results from a phase 2 randomized, double-blind, placebo-controlled trial

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Background and aims: BMS-986263 is a lipid nanoparticle (LNP) containing a small interfering ribonucleic acid (siRNA) that degrades heat shock protein 47 (*HSP47*) mRNA, which encodes HSP47, a collagen chaperone. In the Phase 2 IM025-006 (NCT03420768) study, BMS-986263 weekly (QW) ×12 weeks (wks) was generally well tolerated and demonstrated METAVIR and Ishak improvements in patients (pts) with advanced liver fibrosis from chronic hepatitis C

who had achieved sustained virologic response (HCV-SVR). Here, we present HSP47 target engagement (TE) data (liver *HSP47* mRNA and protein), quantitative fibrosis measurement using dual-photon microscopy (qFIB), and safety through wk 36.

Method: This was a Phase 2, randomised, double-blind, placebo-(PBO) controlled study in pts with METAVIR F3-F4 fibrosis (local liver biopsy) at screening. BMS-986263 (45 or 90 mg) or PBO were IV infused QW ×12 wks; follow-up was until wk 36. Objectives included METAVIR (≥1 stage) and Ishak (≥2 stages) improvements (central-, pair-read liver biopsies); liver *HSP47* mRNA (EDGEseq) changes; HSP47 protein (IHC) and qFIB at wk12; safety and tolerability.

Results: Reduced liver *HSP47* mRNA levels were observed at wk 12 compared with baseline in 13% (2/15; PBO), 44% (8/18; 45 mg), and 71% (20/28; 90 mg) of pts. BMS-986263 45 and 90 mg groups showed a trend for decreased median liver HSP47 protein at wk 12. In IM025-006, 13% (2/15; PBO), 17% (3/18; 45 mg), and 21% (6/28; 90 mg) had METAVIR improvements; 0% (0/15; PBO), 0% (0/18), and 19% (5/27) of 90 mg pts had Ishak improvements. Of pts with METAVIR improvements at wk 12, 50% (1/2; PBO), 67% (2/3; 45 mg), and 100% (6/6; 90 mg) also showed qFIB improvement. All pts with Ishak improvement (5/5, all in the 90 mg group) had improved qFIB. qFIB improvements were observed for some METAVIR and Ishak non-responders. At wk 36, safety findings were consistent with wk 12. Most AEs were mild to moderate infusion-related reactions (IRRs); of all BMS-986263 infusions, IRRs occurred in 7% (15/216; 45 mg) and 11% (37/336; 90 mg) of pts. No meaningful bone biomarker changes occurred.

Conclusion: In this study of a limited number of pts with HCV-SVR and fibrosis, BMS-986263 IV QW ×12 wks demonstrated TE by reducing liver *HSP47* mRNA. The majority of METAVIR and Ishak responders had improved qFIB. BMS-986263 was generally well tolerated through wk 36. These data support further evaluation of BMS-986263 in pts with advanced liver fibrosis.

LBP18

JKB-122 in subjects with non-alcoholic fatty liver disease (NAFLD): a phase 2, randomized, multiple-dose, double-blind, placebo-controlled study

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Background and aims: Non-alcoholic fatty liver (NAFLD) is a growing cause of chronic liver disease worldwide with 25% prevalence rate. NAFLD including nonalcoholic steatohepatitis (NASH), can progress to cirrhosis and hepatocellular carcinoma. These chronic liver diseases become a rapidly growing cause of liver transplantation. JKB-122 is a weak antagonist of the TLR-4, demonstrated to prevent steatosis, inflammation and hepatocellular ballooning in a NASH mouse model. The aim of this study was to assess the safety/tolerability and efficacy of JKB-122 in NAFLD patients with elevated ALT.

Method: This is a randomized (1:1:1), double-blind, placebo-controlled study in adults with NAFLD with an elevated ALT between 1.5× and 5× upper limit of normal. The NAFLD subjects were defined as the presence of hepatic steatosis, either by imaging or histology. Subjects received 5 or 35 mg of JKB-122 or placebo once daily for 3 months. The primary endpoint was reduction in hepatic steatosis by imaging studies and serum ALT at the end of 12-week treatment. The subject was considered as a responder if reduction of hepatic steatosis by image studies along with reduced serum ALT levels either a 30% or more decrease or the ALT value or within the normal range.

Results: 121 subjects were randomized (Mean age, 44 ± 11 years; man, 80%; mean BMI 28 ± 3.3 Kg/m^2; mean liver fat content (LFC) 20.8 ± 8.3%; and mean ALT 103.4 ± 32.7 U/L) and a total of 110 subjects completed all treatment visits and follow-up visit. For primary endpoint by image studies and ALT criteria after 12 weeks treatment, in the per protocol population 11 of 36 subjects, 8 of 37 subjects and 4 of 37 subjects met the definition of a responder in JKB-122 35 mg, 5 mg and placebo arm, respectively. The response rate of JKB-122 35 mg was significantly higher than that of placebo (30.6% vs. 10.8%, p-value = 0.0459). At the end of treatment, mean changes from baseline of fat percentage by magnetic resonance spectroscopy (MRS) were −3.5% ± 5.5%, −1.4% ± 3.3%, and −1.2% ± 4.1% in JKB-122 35 mg, 5 mg and placebo arm, respectively. JKB-122 35 mg and 5 mg arms both had a significant difference in mean change from baseline of fat percentage (p-values = 0.0005 and 0.0144). The LFC reduced >10% absolute rate of JKB-122 35 mg was higher than that of placebo (30.0% vs. 3.8%). JKB-122 35 mg also significantly improve BMI, LDL, HDL, total cholesterol or triglycerides compared to placebo. The most frequent AEs in 35 mg JKB-122-treated patients were dizziness (22% vs 5% in placebo), and most treatment emergent AEs were mild to moderate.

Conclusion: JKB-122 35 mg improves NAFLD in primary efficacy endpoint and some secondary efficacy endpoints, such as ALT, liver fat content in MRS image, cCK-18 level and Enhanced Liver Fibrosis (ELF) score, although no significant inter-group difference was observed compared to placebo. In term of safety profile, JKB-122 was well-tolerated.

LBP19

Obeticholic acid demonstrates sustained improvements at month 24 in transaminases and non-invasive markers of fibrosis: results of a post hoc analysis from the interim analysis of the REGENERATE study

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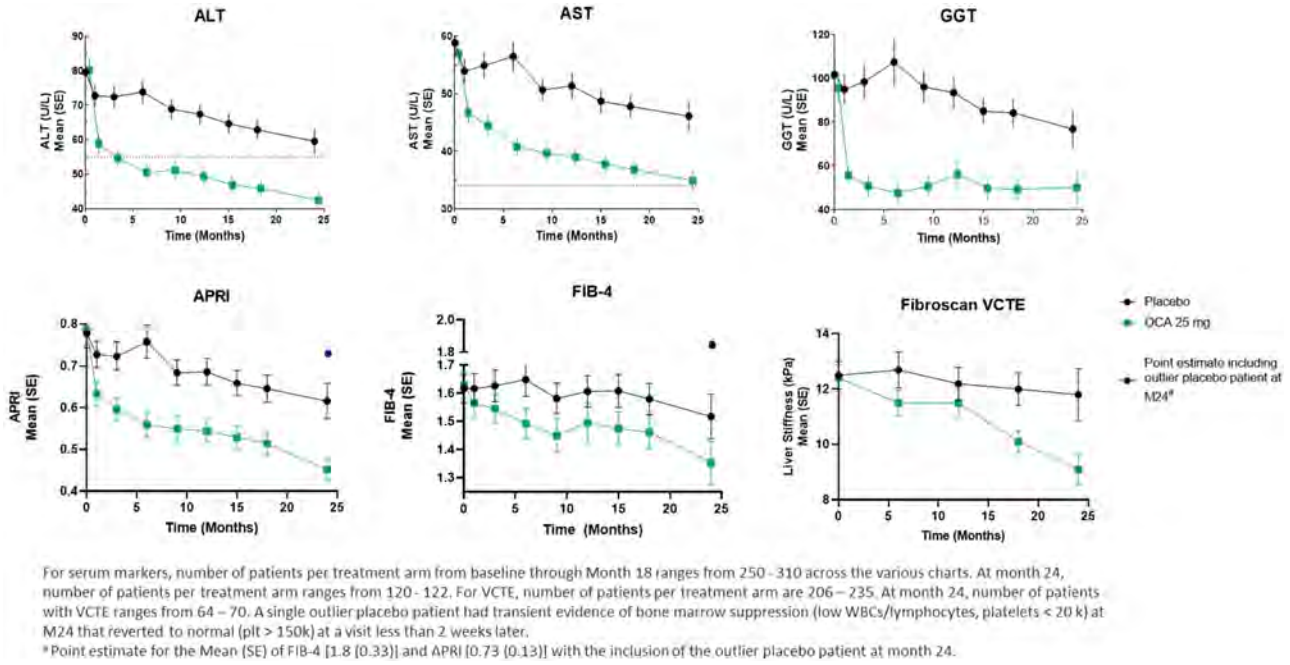
Background and aims: In the REGENERATE (NCT02548351) interim analysis, treatment with obeticholic acid (OCA) improved histologic liver fibrosis in patients with nonalcoholic steatohepatitis (NASH) and advanced fibrosis after treatment for 18 months. The REGENERATE study remains ongoing and will continue through clinical outcomes for verification and description of clinical benefit. To assess durability of response and the relationship between



For serum markers, number of patients per treatment arm from baseline through Month 18 ranges from 250 - 310 across the various charts. At month 24, number of patients per treatment arm ranges from 120 - 122. For VCTE, number of patients per treatment arm are 206 – 235. At month 24, number of patients with VCTE ranges from 64 – 70. A single outlier placebo patient had transient evidence of bone marrow suppression (low WBCs/lymphocytes, platelets < 20 k) at M24 that reverted to normal (plt > 150k) at a visit less than 2 weeks later.
*Point estimate for the Mean (SE) of FIB-4 [1.8 (0.33)] and APRI [0.73 (0.13)] with the inclusion of the outlier placebo patient at month 24.

Figure: (abstract: LBP19)

changes in non-invasive markers and histologic fibrosis improvement, transaminases and non-invasive markers were analyzed in patients with available 24-month data at the planned 18-month interim analysis.

Method: Patients from the interim analysis who had both evaluable month 18 biopsies (N = 250–310 per treatment arm) and month 24 data (N = 120–122 per arm) were included. Changes from baseline to month 24 in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), serum markers of fibrosis (FIB-4, AST to platelet ratio index [APRI]), and liver stiffness (FibroScan® vibration-controlled transient elastography [VCTE]; subset, N = 64–70 per arm) were analyzed. Descriptive summary statistics and percentage changes from baseline over time were evaluated by fibrosis improvement status (improved, stable, worsened) at month 18.

Results: Mean values of transaminases and other serum tests improved rapidly in patients treated with OCA. Improvements were sustained beyond 18 months of therapy compared with placebo (Figure). FibroScan VCTE also demonstrated improvement in liver stiffness over time, with a mean difference of 2.7 kPa between OCA 25 mg and placebo after 24 months on therapy (Figure). Changes in these markers were associated with changes in histologic fibrosis, with the greatest improvements observed in patients who had a ≥1 stage improvement in fibrosis stage at 18 months. Moreover, early changes in these markers were more pronounced in patients who had histologic fibrosis improvement at month 18.

Conclusion: OCA treatment elicited durable improvements in transaminases, other non-invasive serum markers of fibrosis, and liver stiffness by VCTE at month 24, suggesting continued improvement beyond the categorical histologic benefit seen at 18 months.

LBP20

CX3CL1/CXCR1 axis recruits regulatory macrophages to promote tumor recurrence of intrahepatic cholangiocarcinoma after curative surgery

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Background and aims: Background: Intragraft regional immunoregulation on tumor microenvironment may play a critical role in intrahepatic cholangiocarcinoma (iCCA) recurrence after curative surgery. Regulatory macrophages (Mregs) have promising potentials

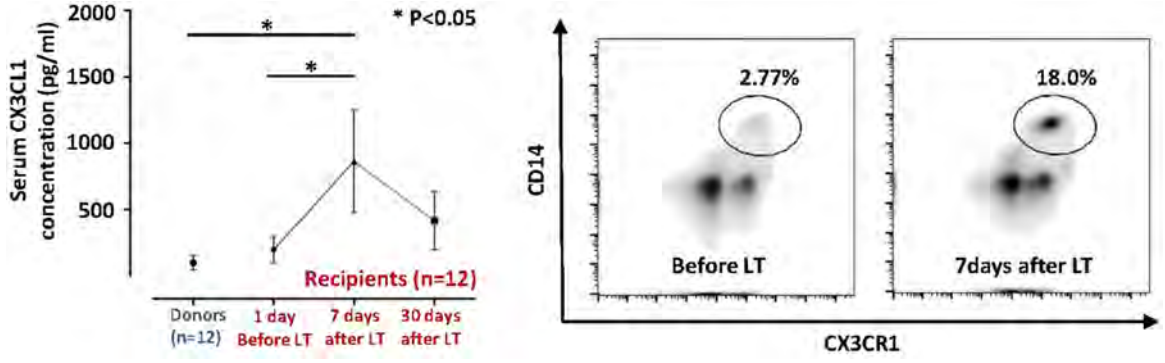

Figure 1: Serum CX3CL1 concentration and peripheral CX3CR1+ monocytes were elevated in LT patients.

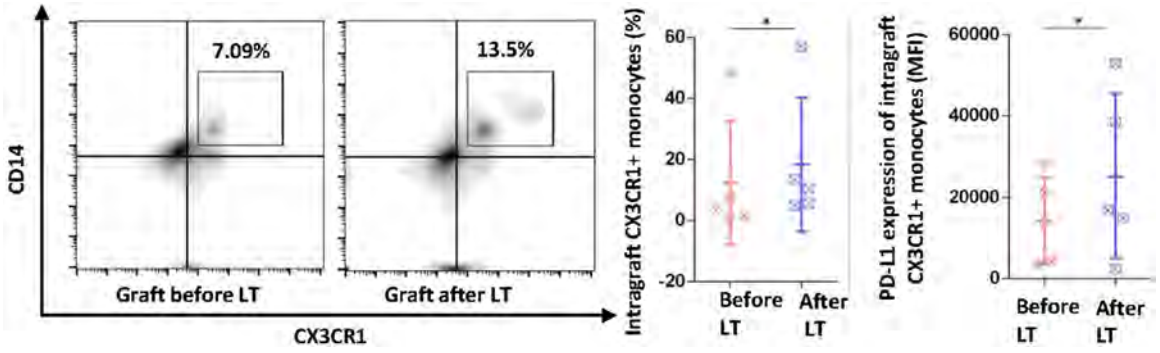

Figure 2: Increased immunosuppressive CX3CR1+ monocytes were detected in the graft of LT patients.

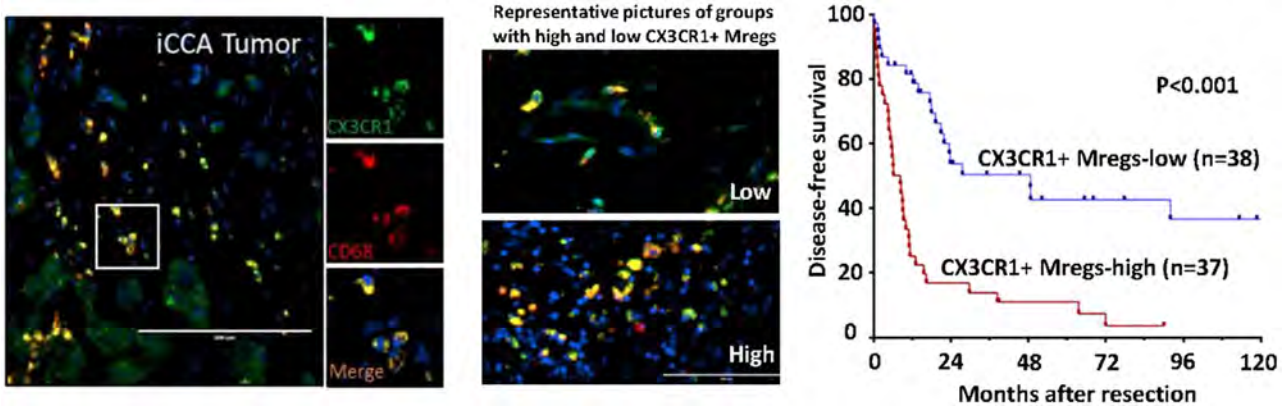

Figure 3: More CX3CR1+ macrophages were correlated with shorter DFS in iCCA.

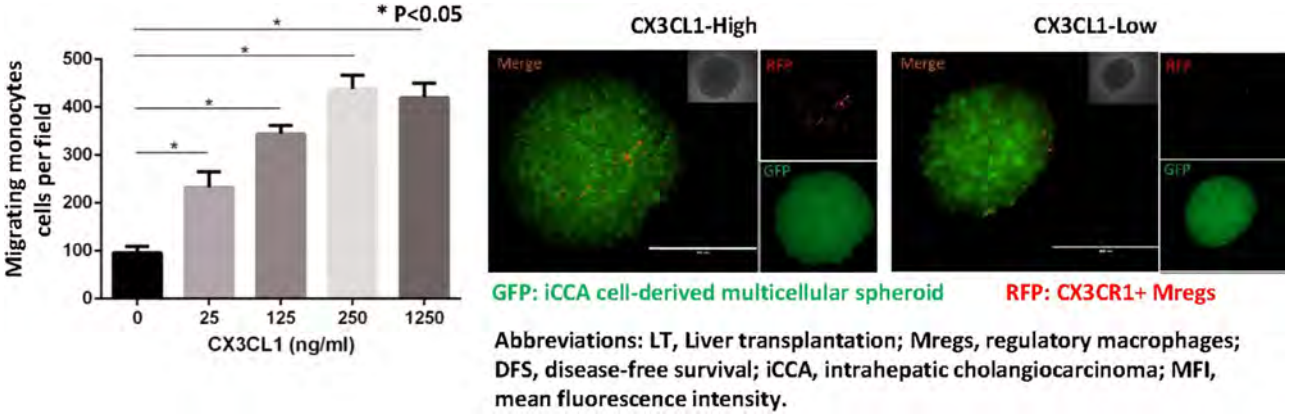

Figure 4: CX3CL1 facilitated the recruitment of monocytes and the infiltration of CX3CR1+ macrophages.

for the treatment of graft rejection due to the potent immunosuppressive function. However, Mregs in the tumor microenvironment were reported to promote tumor growth and immunoevasion. Here, we aim to investigate the role and mechanism of Mregs on iCCA recurrence after curative surgery.

Method: Gene expression profile from our institute and TCGA were analysed to explore the possible link between iCCA and monocytes. The serum CX3CL1 concentration, peripheral and intragraft CX3CR1+ monocytes were assessed in the liver transplant (LT) recipients. A total of 75 patients underwent resection for iCCA was included and prospectively followed-up since 2001 for survival analysis. The phenotypic analyses of Mregs from fresh iCCA tissue were conducted by flow cytometry. The effects of Mregs on iCCA were evaluated in vitro and in humanized NSG mice model.

Results: 1. Elevated serum CX3CL1 concentration and peripheral CX3CR1+ monocytes were detected in post-transplantation patients (Fig.1). 2. Compared with the graft before LT, intragraft CX3CR1+ monocytes and the PD-L1 expression on CX3CR1+ monocytes were increased in the graft after LT (Fig.2). 3. More infiltrated CX3CR1+ Mregs was detected in iCCA tumor tissue both after LT and resection (Fig.3). The higher number of CX3CR1+ Mregs in iCCA tissue was correlated with shorter disease-free survival (DFS) in iCCA patients

after curative surgery (Fig.3); 4. In the multivariate model, CX3CR1+ Mreg was identified as an independent prognostic factor for DFS (HR:3.400, 95%CI: 1.900-6.084, P < 0.001). 4. Elevated CX3CL1 facilitated recruitment and infiltration of Mregs (Fig.4).
Conclusion: Enhanced CX3CL1/CX3CR1 interaction facilitated intrahepatic Mreg infiltration, which subsequently promoted iCCA recurrence after curative surgery.

LBP21

Serum-based Metabolomics-Advanced StEatohepatitis Fibrosis Score (MASEF) fot the non-invasive identification of patients with non-alcoholic steatohepatitis with significant fibrosis

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Background and aims: The burden of non-alcoholic fatty liver disease (NAFLD) is increasing globally. The major priority is to identify patients with non-alcoholic steatohepatitis (NASH) who are at greater risk of progression to cirrhosis, and who will be candidates for clinical trials and emerging new therapies. We aimed to develop a highly specific serum-based score to identify patients with NASH, NAFLD activity score (NAS) ≥4, and significant fibrosis (F2-F3).
Methods: This study included a derivation cohort before validation in multiple international cohorts (n = 908). The derivation cohort was a cross-sectional, multicenter study of patients aged 18 years or older, who underwent liver biopsy for suspicion of NAFLD. To classify those patients with NASH at increased risk, a NAS score of ≥4 (with at least one point on each of steatosis, lobular inflammation and ballooning) and significant fibrosis (F2-F3) were used. The best fitting multivariable logistic regression model was identified and internally validated using boot-strapping. Score calibration and discrimination performance were determined in both the derivation and validation dataset.
Results: We performed serum metabolomic testing in an original cohort of 790 patients that was subsequently blind validated in a derivation cohort of 118 patients. From a total of 289 lipids analyzed, the final MASEF score included only12 lipids, body mass index (BMI), aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Using logistic regression analysis, we could discriminate between NASH patients; NAS≥4 and F2-F3 compared to those without these features. The diagnostic performances of the MASEF score showed an area under the receiver operating characteristic curve (AUC), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 0.81 ± 0.02, 0.36, 0.96, 0.86 and 0.62 respectively, for the mentioned discrimination. While in the derivation cohort the AUC, sensitivity, specificity, PPV, and NPV were 0.82 ± 0.04,0.20, 0.95, 0.62 and 0.75, respectively.

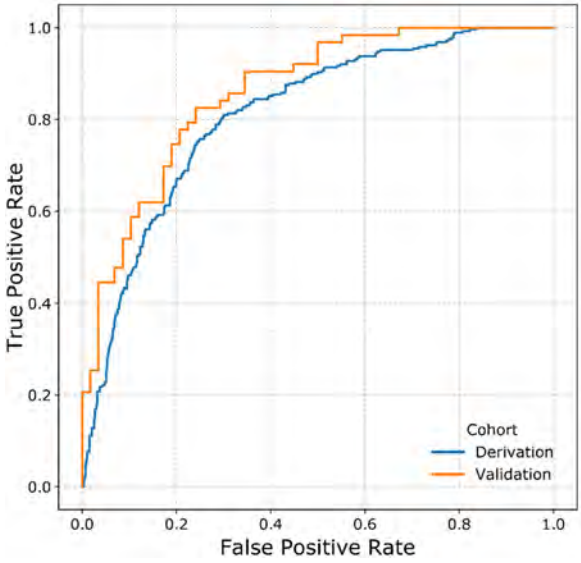

Figure: ROC Curves for the derivation cohort (blue) and validation cohort (orange).

Conclusion: The MASEF score provides an accurate, serum-based, easy to use test to non-invasively identify patients at risk of progressive NASH eligible for clinical trials or treatment.

LBP22

Screening for non-alcoholic fatty liver disease in persons with type 2 diabetes in the U.S. is cost effective: A comprehensive economical analysis

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Background and aims: Globally, the prevalence of non-alcoholic fatty liver disease (NAFLD) is rising. It is imperative to identify high-risk patients whose disease may progress to significant liver fibrosis (≥F2). The American Association for the Study of Liver Diseases (AASLD) has no firm guidelines for non-alcoholic steatohepatitis (NASH) screening in high risk individuals due to inadequate data cost effective and treatment options.
Method: This cost-effectiveness analysis was developed to compare the value of screening in type 2 diabetes (T2D) patients for NASH against not screening. A Markov model was used to conduct a cost-utility analysis of 3 NAFLD screening methods consisting of combinations of ultrasound (US), alanine aminotransferase (ALT) determination followed by (1) liver biopsy alone, or (2) transient elastography for detection of patients more likely to have significant fibrosis (≥F2) followed by liver biopsy or (3) transient elastography alone. Post-detection, patients were hypothetically treated with weight reduction induced by intensive lifestyle intervention (ILI). Data provided by Vilar-Gomez et al. showed that 10% of patients who received the ILI were expected to lose over 10% of their body weight in 12 months. Costs (USD) and quality-adjusted life years (QALYs) were

discounted at 3%; the time horizon is lifetime. The threshold incremental cost-effectiveness ratio (≤$100,000 as well as ≤$50,000 per QALY) used is based on that favored by the Institute for Clinical and Economic Review.

Results: Screening ≥55-year-old patients with T2D/NAFLD using US and ALT, followed by transient elastography, to detect significant fibrosis (≥F2) is a cost-effective strategy versus no screening, when detected patients were immediately treated with a 1-year duration with ILI. Screening with liver biopsy was not cost-effective, because of disutility associated with biopsy.

Results for Screening Strategies with ILI Treatment in Patients with T2D/NASH (≥ F2)

Screening Strategy	Total			Incremental			ICER	
	Cost ($)	QALYs	LYs	Cost ($)	QALYs	LYs	($/QALY)	($/LY)
No screening	29,532	10.99	0.01	851.79	-0.14	0.55	-5,963 (Dominated)	1,556
Strategy 1	30,384	10.85	0.56					
No screening	29,532	10.99	0.01	468.01	-0.06	0.16	-7,222 (Dominated)	2,879
Strategy 2	30,000	10.93	0.17					
No screening	29,532	10.99	0.01	7.93	0.01	0.16	698 (Cost effective)	48
Strategy 3	29,540	11.00	0.18					

Conclusion: Non-invasive screening patients with T2D/NAFLD in the U.S. is cost effective and can be considered to decrease the burden of the disease.

LBP23

CHESS criteria for the screening of varices in patients with compensated advanced chronic liver disease: a multicenter study

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Background and aims: The Expanded-Baveno VI criteria spare more endoscopies than the Baveno VI criteria with a minimal risk of missing varices needing treatment (VNT) in compensated advanced chronic liver disease (cACLD), mainly with hepatitis C virus, alcoholic and nonalcoholic steatohepatitis. This study aimed to validate and optimize the Expanded-Baveno VI criteria in cACLD with hepatitis B virus (HBV) as major etiology.

Method: We enrolled a real-world cohort with cACLD between December 2015 and July 2019 in one university hospital in China (Tianjin Second People's Hospital) to validate the Expanded-Baveno VI criteria. The cohort was also used to study the performance of different thresholds of platelets count and liver stiffness measurement (LSM) for identifying patients at very low risk (<5%) of having VNT to optimize the criteria. The new criteria were validated in an external multicentre cohort between August 2019 and December 2019 in 9 university hospitals in China (161 from The Sixth People's Hospital of Shenyang, 22 from Ankang Central Hospital, 17 from Guangdong Provincial Hospital of Chinese Medicine, 14 from Dalian Sixth People Hospital, 4 from Shanghai Tongji Hospital, 4 from The Fifth Affiliated Hospital of Zunyi Medical University, 2 from Ankang Hospital of Traditional Chinese Medicine, 2 from The People's Hospital of Guangxi Zhuang Autonomous Region, and 1 from The First Hospital of Lanzhou University).

Results: In the real-world cohort of 1085 cACLD with different etiologies (68.0% of HBV), the Expanded-Baveno VI criteria failed to identify patients of having VNT with 35/590 (5.9%) VNT missed. Therefore, the optimized criteria, CHESS criteria (platelet count >105 × 109 cells/L and LSM <19 kPa), were developed with a very low risk (<5%) of missing VNT. The CHESS criteria spared more unnecessary endoscopies than Baveno VI criteria (platelet count >150×109 cells/L and LSM <20 kPa) significantly (50.0% vs. 31.9%, p < 0.001). In addition, the CHESS criteria were validated in the external multicentre cohort of 227 patients with different etiologies (83.7% of HBV), and obviously spared more endoscopies than Baveno VI criteria (51.5% vs. 28.2%, p < 0.001) with 5/117 (4.3%) VNT missed.

	Real-world cohort (N = 1085)	Validation cohort (N = 227)
Age, years	49.83 (11.99)	53.91 (10.01)
Male, n (%)	654 (60.27%)	151 (66.52%)
HBV, n (%)	738 (68.01%)	190 (83.70)
Child-Pugh A, n (%)	974 (89.70%)	215 (94.71)
Platelet count, x10^9 cells/L	141.30 (60.45)	130.42 (57.74)
LSM, kPa	18.32 (13.61)	16.11 (12.29)
VNT, n (%)	139 (12.81%)	30 (13.22%)

Continuous data expressed as mean ± standard deviation. HBV, hepatitis B virus; LSM, liver stiffness measurement; VNT, varices needing treatment.

Conclusion: The CHESS criteria spare more unnecessary endoscopies than Baveno VI criteria with a very low risk of VNT missed in different etiologies (mainly HBV) of cACLD.

LBP24

Post-fecal microbiota transplant taxa correlate with 3-month survival in severe alcoholic hepatitis patients

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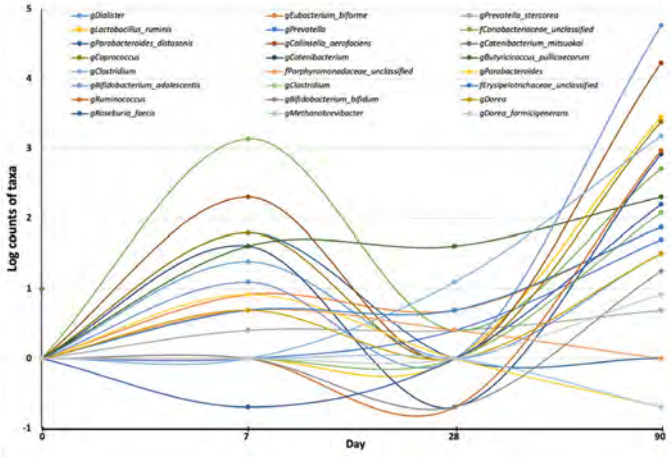
Background and aims: Fecal microbiota transplant (FMT) has been received with mixed outcomes in different diseases. To understand the variations that microbiota has on event-free survival in SAH patients, a randomized controlled trial (NCT03091010) was undertaken comparing FMT with steroid therapy. Results of the microbiota changes are presented; clinical results would be reported separately.

Method: SAH patients (age 18–70 yr) with histological confirmation, DF score >32 and alcohol intake within last 30 days were randomized to receive steroids (n = 57) or FMT (n = 55). FMT was given as fresh preparation via naso-duodenal route for 7 days. Healthy first-degree relatives or those living in the same environment were screened for (but not limited to) *Clostridium difficile* toxin, *Helicobacter pylori* stool antigen (Ag), *Cryptosporidium* and *Isospora*, Rotavirus Ag, HBsAg, anti-HCV, HIV 1 and 2, VDRL and HLA A1. Microbiota was assessed by sequencing V3-V4 region of 16 s gene from DNA isolated from stool samples collected at baselines, days 7, 28, 90, on MiSeq system, using 2 × 300 bp paired-end mode.

Results: Patients in steroid and FMT groups were comparable at baseline (DF score 65 ± 16.2 and 68 ± 14, p = NS). FMT showed better outcome compared to steroid therapy for 90 days survival (p = 0.005).

Taxa like *Lactobacillus ruminis, Collinsella aerofaciens, Butyricicoccus pullicaecorum, Bifidobacterium adolescentis, Ruminococcus sp, Bifidobacterium bifidum, Roseburia faecis* and *Dorea formicigenerans* were not detected at baseline but were introduced by donors and took about 14–28 days to establish (Figure). In FMT arm, the Phylum Tenericutes was significantly associated with mortality (p = 0.003). Pathogenic genera like *Klebsiella*, *Salmonella*, and *Mycoplasma* showed significant increase (p = 0.075, 0.011, 0.037, 0.025 respectively) in non-survivors. Proteobacteria and Fusobacteria were significantly (p < 0.001, 0.019 respectively) associated with mortality. Phylum Firmicutes, family Lachnospiraceae, and genera *Veillonella* and *Prevotella*, favoured survival (p = 0.008, 0.051, 0.045, 0.033, respectively). There were no significant adverse events with FMT.



Conclusion: Healthy donor FMT is safe in SAH patients, establishes beneficial flora within 4 weeks and improves 90-day survival. However, in non-survivors pathogenic phyla persist. Taxa associated with mortality need to be studied and continuously screened for, to add FMT from new healthy donors, to improve survival.

LBP25

A novel immunoregulatory role for complement receptor C3AR1 in fibrosing cholangiopathies of biliary atresia and primary sclerosing cholangitis

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Background and aims: The fibrosing cholangiopathies, biliary atresia (BA) and primary sclerosing cholangitis (PSC), are characterized by cholangiocyte injury, immune cell infiltrations and obstruction or stricturing of the biliary tree. The complement receptor, C3AR1 is implicated in negative regulation of immune cell mobilizations and suppression of *Tnfa* and *Il1b* in liver injury. Here, we investigated regulation of biliary disease pathogenesis by C3AR1 in the context of BA and PSC.

Method: Human and murine RNASeq mRNA expressions and proteomics data were analysed for plasma C3, C3a and C3adesArg. Experimental BA was induced in newborn wild-type (WT) and C3AR1$^{-/-}$ mice by *i.p.* injection of 1.0×10^6 ffu of rhesus rotavirus (RRV) and phenotyped for cholestasis. Double knockout mice were generated by superimposing C3AR1 deficiency on an MDR2$^{-/-}$ background. Homozygous MDR2$^{-/-}$C3AR1$^{-/-}$, WT and MDR2$^{-/-}$ mice were sacrificed on day 70 of life. Liver biochemistry was assessed by plasma bilirubin, ALT and AST levels. Histology of extrahepatic bile ducts (EHBDs) and livers was evaluated by H&E staining and cytokeratin (CK)$^+$ bile duct profiles. Liver immune cells were phenotyped using flow cytometry and gene expressions were determined by qRT-PCR.

Results: mRNA expressions of C3AR1, CXCR4 and CXCL12 were elevated in livers of human (2.5–7.3 fold above normals $P \leq 0.0003$) and EHBDs of experimental BA (RRV: 1.3–6.3 fold above controls, $P < 0.02$) reflecting homeostatic anti-inflammatory responses. Serum levels of C3, C3a and C3adesArg also increased in patients with BA (1.2–1.4 fold above controls, $P < 0.03$). RRV infection of C3AR1$^{-/-}$ mice resulted in severe EHBD atresia (Figure 1A), liver necroinflammation, early mortality by day 10 (77%) *vs* WT mice (0%, $P < 0.0001$) and elevated serum total bilirubin (25.7 ± 3.9; WT: 13.1 ± 1.9 mg/dL) and ALT (354 ± 158; WT: 128 ± 16 IU/L) levels ($P < 0.0001$). Hepatic mRNA expressions of *Tnfa*, *Il1b* and *Il6* and Nkg2d$^+$ CD4$^+$/CD8$^+$, NK, pDCs, macrophage and neutrophils were significantly elevated (2.6–6.3 fold, $P < 0.01$–<0.0001) in RRV–C3AR1$^{-/-}$ mice. Importantly, RRV infection suppressed C3AR1 expression on hepatic CD45$^+$Lin$^+$ and increased on CD45$^-$Lin$^-$ cells. MDR2 deficiency significantly suppressed hepatic C3AR–expressing CD3$^+$CD314$^+$CD4$^+$/CD8$^+$, CD11b$^+$Gr1$^+$, pDC and NKp46$^+$CD314$^+$ cells. C3AR1$^{-/-}$MDR2$^{-/-}$ mice showed enhanced onion skin fibrosis, dilatation of intrahepatic ducts resembling large-duct PSC and an inflamed and tortuous extrahepatic common duct (Figure 1B). Sirius red areas increased significantly in C3AR1$^{-/-}$MDR2$^{-/-}$($1.6^{E+05} \pm 4.4^{E+04}$) compared to MDR2$^{-/-}$ mice ($7.4^{E+04} \pm 3.3^{E+04}$).

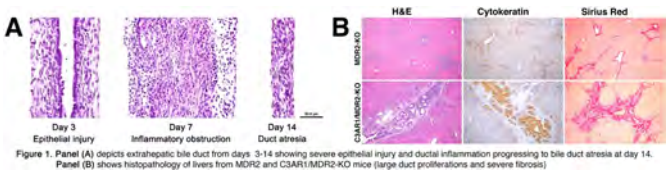

Figure 1. **Panel (A)** depicts extrahepatic bile duct from days 3-14 showing severe epithelial injury and ductal inflammation progressing to bile duct atresia at day 14. **Panel (B)** shows histopathology of livers from MDR2 and C3AR1/MDR2-KO mice (large duct proliferations and severe fibrosis)

Conclusion: C3AR1 regulates the fibroinflammatory and proliferative responses in biliary atresia and primary sclerosing cholangitis. C3AR1 agonism may therefore be a novel therapeutic intervention in pediatric and adult cholestatic liver diseases.

LBP26

Resolution of non-alcoholic steatohepatitis and hepatic fibrosis by sodium glucose transporter-2 inhibitor, ipragliflozin; a multicenter randomized controlled trial

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Background and aims: Sodium glucose transporter-2 inhibitors (SGLT2) are now widely approved treatment against diabetes, whereas the effect on hepatic outcome of nonalcoholic fatty liver disease (NAFLD) remains uncertain. We aimed to evaluate the SGLT2 effect on pathogenesis of NAFLD including pathological findings.
Method: Multicenter randomized controlled trial was conducted and diabetic patients with NAFLD were included. Liver biopsy was performed before randomization and 2nd liver biopsy was performed after the treatment for 72 weeks with ipragliflozin (50 mg/day, n = 21; IPR) or active control treatment, except SGLT2, pioglitazone, and/or glucagon-like peptide-1 analogs (n = 25; CTR). All liver biopsies were evaluated by two pathologists who were blind to group assignment and clinical parameters. Nonalcoholic steatohepatitis (NASH) was diagnosed using Matteoni's classification.
Results: There were no significant differences in basal bodyweight, hemoglobin A1c, frequency of concomitant diseases, or pathological NAFLD findings between the groups. Hepatic fibrosis was observed in 17 patients (81%) of IPR and 18 patients (72%) of CTR. After the treatment, IPR showed more significant decrease in body weight, BMI, visceral fat area evaluated by CT scan and hemoglobin A1c comparing with CTR. Liver fibrosis improved in 70.6% (12/17) of patients with liver fibrosis in the IPR group and 22.2% (4/18) of those in the CTR group ($p < 0.01$). Improvement in hepatocyte ballooning was greater in IPR than CTR (52.4% vs. 24%, $p < 0.05$). There was no significant difference between the groups in steatosis. NASH resolution was obtained in 66.7% of NASH patients of IPR and 27.3% of those of CTR. There was no patient with development to NASH from non-NASH in IPR whereas 33.3% of non-NASH patients developed to NASH in CTR.
Conclusion: Long term ipragliflozin treatment ameliorates hepatic fibrosis of NAFLD. Ipragliflozin brings NASH resolution and prevent aggravation of non-NASH, as well as improve glycemic control and obesity. SGLT2 inhibitor could be a therapeutic choice of diabetic patients with NAFLD.

LBP27

Novel markers to predict virological and clinical relapse onset following antiviral treatment discontinuation in chronic hepatitis B patients

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Background and aims: This observational study aims to identify virological and host genetic predictive markers for relapse onset in chronic hepatitis B (CHB) patients discontinuing direct antiviral treatment.
Method: This multi-center, prospective study in Taiwan enrolled 186 CHB patients in their last year of a minimum 3-year treatment regimen with direct antivirals. Patients were followed for up to 2 years after treatment discontinuation. Virological relapse (VR) was defined as HBV DNA >2000 IU/mL. Clinical relapse (CR) was defined as ALT level >2× the upper limit of normal in addition to VR.
Blood samples were collected for DNA profiling by whole genome genotyping (Affymetrix Axiom™ Asia Precision Medicine Research Array).
Results: Of the cohort, 161 (86.6%) patients experienced VR of whom 110 (59.2%) also had a CR. HBeAg negativity prior to the start of treatment was associated with earlier VR. High HBsAg levels (≥100 IU/mL) at the end of the treatment (EoT) period was associated with earlier onset of VR and CR. Entecavir treatment was associated with delayed VR and CR compared to tenofovir.
A genome-wide association study revealed 33 independent genetic markers significantly associated with onset of VR and 9 markers significantly associated with onset of CR. Amongst those markers, SNPs in *CTLA4*, *HLA-DPB1* and *RBFOX1* (reported earlier as a recurrent site for HBV integration) were found to be associated with onset of CR, and SNPs in *SLC10A1* (encoding HBV receptor NTCP), *FUT8* (regulating NTCP expression) and several SNPs in the *HLA-C* region with onset of VR after treatment discontinuation.
Clearly improved sensitivity and specificity of the Cox proportional hazard regression models was observed when adding genetic markers to HBsAg level at EoT, antiviral treatment regimen, and HBeAg status at the beginning of the last treatment regimen. The Receiver Operating Characteristic (ROC) AUC increased from 0.67 to 0.86 to predict CR within 6 months after EoT, and from 0.82 to 0.95 to predict VR within 3 months after EoT.
Conclusion: The study revealed novel genetic markers predictive of relapse onset after treatment discontinuation. Several identified genes have previously been described already as key player in HBV replication but are now for the first time also shown to be associated with time to relapse in CHB. Host genetic markers can be useful contributors in predicting patient outcome when considering stopping suppressive treatment.

LBP28

Noninvasive point-of-care 13C-Methacetin Breath Test (MBT) predicts risk of clinical deterioration independently of currently used prognostic indicators in patients with decompensated NASH cirrhosis

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Background and aims: Patients with decompensated NASH cirrhosis are at risk for subsequent worsening of liver function and portal hypertension, resulting in decompensation events such as ascites (ASC), variceal hemorrhage (VH) and hepatic encephalopathy (HE). MBT quantitates hepatic CYP1A2 metabolism of orally ingested, non-radioactive ^{13}C-methacetin to $^{13}CO_2$ and acetaminophen by continuous monitoring of the $^{13}CO_2/^{12}CO_2$ ratio in expired breath. MBT provides composite results integrating the impacts of hepatic metabolic function and perfusion that quantifies the status of "liver health." The aim was to prospectively validate the independent association of MBT with the risk of developing a composite hepatic deterioration endpoint (Event) comprised of new ASC, VH, new HE, MELD score progression (MSP, defined as increase ≥4 points from baseline), and all-cause mortality (ACM) in patients with

decompensated NASH cirrhosis enrolled in a randomized, placebo-controlled trial of the caspase inhibitor emricasan.
Method: MBT was measured with the Exalenz BreathID® System using a cut-off value identified in a previous study. MBT results were collected at baseline from 138 patients enrolled in the study. Prospective monitoring for Events was performed for a median of 315 days. Results of MBT, expressed as the maximal ^{13}C-methacetin percent dose recovery rate (PDRpeak), reflect the peak hepatic capacity to metabolize methacetin.
Results: Average age was 61.1 (SD:8.5) years; average BMI was 33.9 (SD:6.2) kg/m^2; 52.2% were female. During the observation period, 38 patients (27.5%) met the composite endpoint (25 MSP, 1 HE, 1 ASC, 7 VH, 4 ACM). The previously identified cutoff of PDRpeak ≤5.5%/h identified 15.2% of all patients as having a high risk of Events and included 11/38 Events with a hazard ratio (HR) of 4.2 (95% CI: 1.75–10.07, p = 0.001) for Events (Figure). Multivariate analyses showed that the PDRpeak ≤5.5%/h had an independent predictive value superior to currently used predictors such as MELD or CTP scores (either separately or combined) or previous decompensation.

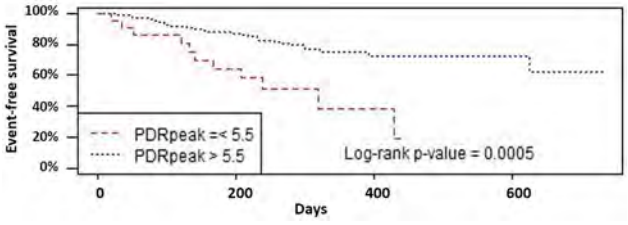

Figure: Event-free survival Kaplan Meier curve for MBT PDRpeak cutoff of 5.5%/h.

Conclusion: In patients with decompensated NASH cirrhosis, baseline MBT identified patients at high risk for additional clinical deterioration Events independently and more accurately than either MELD or CTP. The data indicate that MBT is a safe, operator-independent, in-office, non-invasive point-of-care tool to identify patients at increased risk for clinical deterioration.

LBP30

Antiviral activity and safety of the hepatitis B core inhibitor ABI-H0731 administered with a nucleos(t)ide reverse transcriptase inhibitor in patients with HBeAg-positive chronic hepatitis B infection in a long-term extension study

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Background and aims: ABI-H0731 (731) is a first-generation HBV core inhibitor in development for the treatment of chronic hepatitis B infection (CHB). In the Phase 2a studies 202 and 201, treatment naïve (TN) and virally suppressed (VS) HBeAg-positive patients (pts) with CHB were randomized 1:1 to 731 or placebo (Pbo) with NrtI in a blinded manner for 24 weeks. The combination of 731+NrtI was well tolerated and demonstrated faster and greater reductions in HBV DNA and pgRNA than NrtI alone. Following study completion, eligible pts entering an open-label extension study 211 received 731+NrtI for up to an additional 76 weeks. Here we report the updated data from study 211 through the current last reported observation.
Method: For TN pts, HBV DNA was measured by COBAS TaqMan 2.0 (LLOQ = 20 IU/mL) and pgRNA by an in-house quantitative PCR assay (LLOQ = 135 U/mL). For VS pts, HBV DNA was measured by an in-house semi-quantitative PCR assay (LLOD = 5 IU/mL) and pgRNA by an in-house semi-quantitative RT-PCR assay (LLOD = 5 IU/mL). For all pts, quantitative HBeAg and HBsAg were measured by Abbott Architect (LLOQ = 0.11 IU/mL and 0.05 IU/mL, respectively) and HBcrAg by Lumipulse G (LLOD = 1 kU/mL). Safety was assessed by adverse events (AEs) and laboratory parameters.
Results: Of the 23 TN pts from study 202, median (range) treatment duration 57 (36–83) weeks, 21 pts have DNA declines to <100 IU/mL and 6 pts have pgRNA declines to <500 U/mL. Declines of ≥1 log or at <LLOQ in HBeAg, HBcrAg and HBsAg have been observed in 6, 8 and 3 pts, respectively. Of the 43 VS pts from study 201, median (range) treatment duration 58 (30–81) weeks, 34 and 21 pts have now achieved DNA and pgRNA <5 IU/mL, respectively. In addition, 29 pts have HBeAg <5 IU/mL, 27 pts have HBcrAg <500 kU/mL and 4 pts have HBsAg <1000 IU/mL. During the first 24 weeks of study 211, AEs were reported by 47% (31/66) pts, most of which were Grade 1 or 2. There were no SAEs or AEs leading to study drug discontinuation. The only AE reported by >5% was upper respiratory tract infection (4 pts, 6%). Most laboratory abnormalities were Grade 1 or 2. Transient or intermittent Grade 3 elevations in ALT were observed in 2 pts (3%), both of whom continue on study drug.
Conclusion: Results from the ongoing Phase 2a extension study demonstrate continued declines in HBV DNA, pgRNA and viral antigens in pts treated with 731+NrtI. 731 continues to exhibit a favorable safety and tolerability profile in pts treated for over 1 year. The data support the continued development of 731.

LBP31

Machine learning identifies histologic features associated with regression of cirrhosis in treatment for chronic hepatitis B

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Background and aims: Machine learning (ML) may facilitate interpretation of histologic changes associated with treatment of chronic hepatitis B virus (HBV) infection. We developed ML models

that identify and quantify histologic features in a clinical study of HBV patients receiving antiviral therapy.
Method: ML models were developed using H&E histology images from 330 patients enrolled in registrational studies for tenofovir disoproxil fumarate for HBV (GS-US-174-0102, GS-US-174-0103). Histological improvement and regression of cirrhosis were assessed by a central pathologist at baseline (BL) and weeks 48 and 240 according to the Ishak/Knodell necroinflammatory scoring and Ishak fibrosis staging systems. Images were split into training (N = 1090) and testing sets (N = 1061). Models were trained using the PathAI research platform (Boston, MA) to identify inflamed regions and immune cells (lymphocytes and plasma cells) using annotations from 40 board-certified pathologists. Additional annotations of steatosis and ballooning from previous models were included in training. Slide-level, quantitative ML features were computed and correlated with pathologist scores to assess accuracy. Regression analysis was performed to determine associations of ML features at BL and changes from BL with cirrhosis regression at week 240. Results were generated using the testing image set.
Results: ML % area of portal inflammation correlated strongly with Ishak portal inflammation scores ($\rho = 0.643$; $p < 0.001$) and ML % area of interface inflammation correlated strongly with Ishak periportal necrosis scores ($\rho = 0.716$; $p < 0.001$). Of the 48 patients in the testing set with cirrhosis at BL, 36 patients (75%) no longer had cirrhosis at week 240. Lower ML % area of steatosis (Figure) and greater ML % area of lobular inflammation at BL were predictive of cirrhosis regression ($p = 0.006$, $p = 0.047$, respectively), indicating the presence of underlying fatty liver in those who do not resolve cirrhosis. Change from baseline in ML % area of portal and lobular inflammation as well as change in lymphocyte density correlated with regression of cirrhosis at week 240 ($p = 0.010$, $p = 0.026$, $p = 0.031$ respectively).

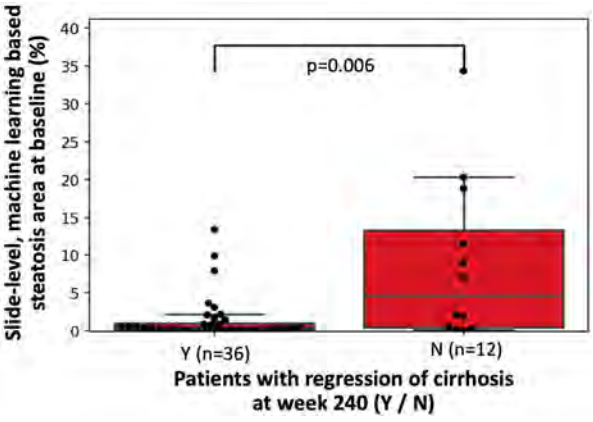

Figure: Steatosis area at baseline, determined by machine learning, was predictive of cirrhosis regression at week 240.

Conclusion: An ML approach accurately classified histopathologic features in H&E images from HBV clinical trial biopsies. ML features at BL and changes in ML features with treatment were significant associated with cirrhosis regression. An ML approach for evaluating liver histology in patients with HBV can provide mechanistic insight into both HBV disease pathogenesis and cirrhosis regression.

LBP32

Long-term survival of repeat hepatic resection and radiofrequency ablation for patients with recurrent hepatocellular carcinoma: a multicentric study

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Background and aims: The long-term survival of repeat hepatic resection (rHR) and radiofrequency ablation (RFA) for patients with recurrent hepatocellular carcinoma (HCC) is still unknown. We did a multicentric study to assess the long-term survival of rHR and RFA for patients with recurrent HCC.
Method: Between January 01, 2006, and December 31,2017, 940 patients with recurrent HCC received rHR orRFA. Only those with recurrent HCC within Milan criteria (with a solitary nodule diameter of ≤5 cm; 3 or fewer nodules, each ≤3 cm in diameter; and no macrovascular invasion or distant metastasis) after initial hepatic resection and had Child-Pugh liver function class A or B (7 score) werer included. The median (range) follow-up time was 65.6 (1.3–152.8) months.
Results: 847 patients from 9 centres in mainland China, Hongkong, and Italy were enrolled in the study. Of these, 307 patients received rHR while 540 received RFA. Median overall survival was 73.5 months in patients treated with rHR, compared with 66.3 months in those who received RFA (hazard ratio [HR] 0.99 [95% CI 0.80–1.24]; $p = 0.969$). The corresponding 10-years overall survival of the two groups were 34.8% and 28.3%. Median recurrence-free survival was significantly longer in rHR group when compared with the RFA group (24.1 months vs 15.2 months; HR 0.75 [0.63–0.88]; $p < 0.001$). The corresponding 10-years recurrence-free survival of the two groups were 13.1% and 6.0%. However, patients in the RFA group were with lower perioperative mortality and morbidity rates, and shorter hospital stay. Subgroup analyses based on each center and propensity score analysis found similar findings.

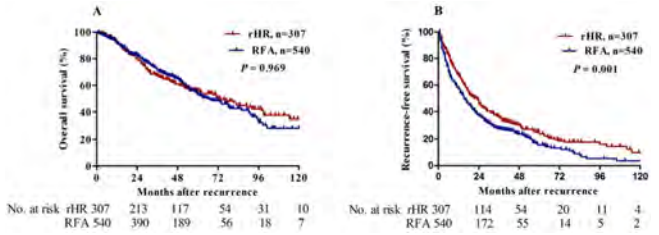

Figure 1. Overall survival (A) and recurrence-free survival (B) after repeat hepatic resection (rHR) or radiofrequency ablation (RFA) for recurrent HCC within Milan Criteria in total population.

Conclusion: rHR is associated with better recurrence-free survival for patients with recurrent HCC within Milan criteria. However, RFA is associated with lower mortality and morbidity rates with similar long-term overall survival. It could be considered as a reasonable alternative in patients with high risk for rHR.

LBP33

Analysis of HBsAg levels, HBsAg isoforms, HBsAg immune complexes, HBV pregenomic RNA and HBcrAg dynamics during and after NAP-based combination therapy in the REP 301-LTF and REP 401 studies

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Background and aims: After completion of NAP-based combination therapy with pegIFN and follow-up in the REP 301-LTF study (3.5 years) and REP 401 study (48 weeks), combined HBV outcomes were functional cure (HBsAg <0.05 IU/mL, HBV DNA target not detected, normal ALT [FC]) in 18/52 (35%), virologic control (HBV DNA ≤2000 IU/mL, normal ALT [VC]) in 19/52 (36%) and rebound (R) in 15/52 (29%) of participants. The goal of this study was to analyze the relationship between HBV outcome and experimental virologic markers of HBV infection.
Methods: Frozen serum samples (n = 1153) from all 52 participants in the REP 301/REP 301-LTF and REP 401 studies were analyzed by the following:

1. Abbott ARCHITECT HBsAg NEXT (analytical sensitivity 0.005 IU/mL).
2. Abbott research use only (RUO) assays for HBsAg isoforms (large, medium, small).
3. Abbott RUO assay for HBsAg/anti-HBs immune complexes (HBsAg IC).
4. Abbott RUO assay for pregenomic HBV RNA (pgRNA).
5. Fujirebio HBcrAg (LLOQ 3log$_{10}$ U/mL).

Results: All participants experiencing HBsAg loss (<0.05 IU/mL) during therapy (28/52) rapidly became negative with HBsAg Next. HBsAg <0.005 IU/mL was confirmed at the end of follow-up in 18/18 functional cure and 1/1 virologic control participants with previous HBsAg <0.05 IU/mL.
A more rapid reduction of S-HBsAg relative to the reduction of other HBsAg isoforms occurred in 39/40 participants with HBsAg decline >2 log$_{10}$ from baseline, consistent with targeting SVPs. At the end of follow-up, HBsAg isoforms were detectable in 0/18 (FC), 17/19 (VC) and 15/15 (R) participants. HBsAg IC (relative luminescence units or RLU) were in the positive range in 30/52 participants at baseline and at the end of follow-up in 0/18 (FC), 5/19 (VC) and 10/15 (R) participants.
At baseline, HBV RNA and HBcrAg were present in 42 and 34 participants. HBV RNA loss on therapy occurred in 5/ 14 (FC), 5/16 (VC) and 1/12 (R) participants. HBcrAg < LLOQ on therapy occurred in 5/9 (FC), 7/15 (VC) and 3/10 (R) participants. At the end of follow-up, both HBV RNA and HBcrAg were > LLOQ in 1/18 (FC), 15/19 (VC) and 13/15 (R) participants.
Conclusion: Functional cure of HBV infection following NAP-based combination therapy is profound, with HBsAg <0.005 IU/mL and both HBV RNA and HBcrAg < LLOQ. NEXT negativity and the absence of HBsAg IC RLUs in the positive range at the end of follow-up in FC participants suggests efficient reduction in integrated HBV DNA.

NAFLD: Clinical aspects except therapy

THU001

Adipose tissue insulin resistance and inflammation, but not reduced hepatic fat oxidation, are associated to active NASH and severe fibrosis

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Background and Aims: The mechanisms that are involved in the progression of steatosis (NAFL) to NASH and to advanced liver disease are not completely elucidated. Reduced liver mitochondrial fat oxidation and VLDL secretion as consequences of increased fat overflow to the liver are implicated. Thus, we hypothesized that subjects with more severe NAFLD/NASH are those with increased adipose tissue (AT) insulin resistance (Adipo-IR, reflecting the impaired suppression of lipolysis), reduced beta hydroxybutyrate (BOH, reflecting hepatic mitochondrial fat oxidation) and reduced apolipoprotein B (ApoB), a rate limiting factor for VLDL secretion and thus implicated in the secretion of hepatic triglyceride (TG).
Method: In 318 histologically characterized NAFLD subjects (188 of which had NASH) in the EPoS European NAFLD Registry we measured circulating markers of AT dysfunction i.e., free fatty acid (FFA) and Adipo-IR = FFAxIns, AT inflammation (i.e. leptin, adiponectin, TNF-α and MCP-1), hepatic lipid oxidation (BOH) and secretion (TG and ApoB). Data were analysed by logistic multivariable analysis (LMA) adjusted for age, gender and BMI and odd ratios (OR) were calculated.
Results: Subjects with NASH had higher BMI (32.9 ± 0.4 vs 31.1 ± 0.6 Kg/m^2), Adipo-IR = FFAxIns (23.2 ± 1.5 vs 16.3 ± 1.6), TNF-α (4.9 ± 0.2 vs 3.3 ± 0.2 pg/ml), MCP-1 (112 ± 3 vs 92 ± 3 pg/ml), leptin (13.8 ± 1.0 vs 10.4 ± 1.0 ng/ml) and reduced adiponectin (11.0 ± 0.6 vs 13.5 ± 0.8 ug/ml), all p < 0.001 while TG (213 ± 37 mg/dl), ApoB (77 ± 2 mg/dl), BOH (99 ± 9 umol/l) and FFA (0.76 ± 0.02 mmol/l) were similar in the two groups.
Dysfunctional AT (showed by increased Adipo-IR) was independently associated with increased steatosis (OR = 8.3), presence of active NASH (OR = 3.1) and fibrosis F3-F4 (OR = 2.5), all p < 0.001.

Surprisingly, hepatic mitochondrial fat oxidation, reflected by BOH, was not reduced, but rather increased in subjects with F3-4 and associated with adipo-IR, ie with the overflow of fat from the adipose tissue to the liver ($p < 0.0001$). Adipo-IR was strongly positively correlated also with TG, leptin, TNF-α and MCP-1 concentration ($p < 0.0001$).
Conclusion: Severity of NAFLD is strongly associated with markers of AT dysfunction and inflammation while mitochondrial beta oxidation does not appear to be dysfunctional, indicating once again the importance of AT in the progression of NAFL to NASH.

THU002
Natural history and prognostic factors of compensated cirrhosis secondary to non-alcoholic steatohepatitis in Catalonia
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Background and Aims: Most of the studies evaluating natural history of cirrhosis have been performed in patients with alcoholic liver disease or viral hepatitis. There is scarce information about natural history of patients with cirrhosis due to nonalcoholic steatohepatitis (NASH). The aim of the present study was to evaluate the natural history and prognostic factors in cirrhosis due to NASH.
Method: Retrospective study of patients with cirrhosis due to NASH in 9 hospitals from Catalonia. All patients diagnosed of NASH-cirrhosis between January 2010 and January 2019. The diagnosis of NASH cirrhosis was made according to clinical, analytical, imaging, elastographic and/or histologic criteria. Development of complications of cirrhosis, cardiovascular events, cancer or death were evaluated during follow-up.
Results: 446 patients with NASH-cirrhosis were identified. Among those, 382 were compensated at diagnosis and constitute the study population. Mean age at diagnosis was 65 ± 10 years, 51% were women and BMI was 32 ± 6 Kg/m^2. At diagnosis, 93% of patients had some metabolic risk factor, 65% had imaging signs of portal hypertension and 49% had esophageal varices. Mean liver stiffness value was 26 ± 16 kPa. The mean follow-up time was 3.6 ± 2.4 years. Ninety-two patients (24%) developed at least one complication of cirrhosis, being the most frequent ascites (18%), encephalopathy (9%), acute kidney injury (9%), gastrointestinal hemorrhage (8%) and spontaneous bacterial peritonitis (2%). Nine percent of patients developed hepatocellular carcinoma. During follow-up 37 patients died (10%). The most frequent cause of death was complications of cirrhosis (33%), followed by extrahepatic cancers (11%) and cardiovascular diseases (8%). Patients who died were older, had higher hepatic venous pressure gradient, higher liver stiffness, worse liver function and, interestingly, lower BMI compared to those who survived. The only parameters independently associated with mortality during follow-up were increased liver stiffness [OR 1.04 (1.02–1.07); $p = 0.002$] and lower BMI [OR 0.88 (0.78–0.99); $p = 0.03$].
Conclusion: Patients with NASH-cirrhosis in our cohort were diagnosed at advanced ages, had a similar distribution among genders and had a high prevalence of metabolic risk factors. Most common decompensation was ascites and the first cause of death was liver-related. High liver stiffness and low BMI were directly correlated with mortality.

THU003
Non-alcoholic fatty liver disease fibrosis score predicts cardiovascular mortality in post percutaneous coronary intervention patients: 5-year results from an observational registry
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Background and Aims: The nonalcoholic fatty liver disease fibrosis score (NFS) is comprised of metabolic risk indicators that may accurately predict residual cardiovascular risk in patients with coronary artery disease (CAD) and metabolic dysfunction.

Table 1 Univariable and multivariable analysis for the association with LV dysfunction

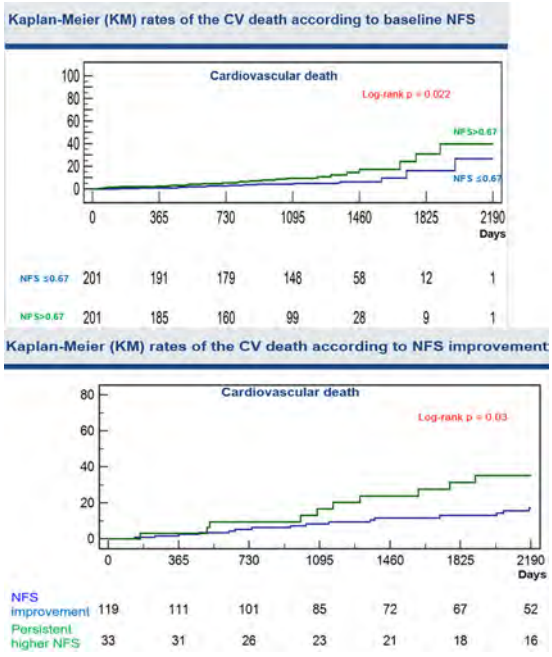
Variables	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
Age	1.45 (1.03 to 1.94)	0.032	1.14 (1.04 to 2.04)	0.046
gender	0.71 (0.47 to 1.07)	0.104	1.18 (0.68 to 2.04)	0.558
diabetes	1.22 (1.96 to 1.51)	0.091	1.50 (0.90 to 2.50)	0.124
Hypertension	1.18 (0.68 to 2.04)	0.558		
Body Mass Index	1.50 (0.90 to 2.50)	0.124		
baseline high NFS>0.67	2.63 (1.64 to 4.21)	<0.001	1.86 (1.36 to 2.55)	< 0.001

Table 2 Multivariable Cox regression models for cardiovascular death

Models 1	Adjusted HR (95% CI)	p
Age	1.45 (1.03 to 1.94)	0.032
gender	0.71 (0.47 to 1.07)	0.104
diabetes	1.49 (1.09 to 2.04)	0.015
baseline LVEF<40%	2.20 (1.53 to 3.15)	<0.001
baseline high NFS>0.67	1.42 (1.03 to 1.95)	0.023
Model 2		
Age	1.33 (0.94 to 1.87)	0.108
gender	1.26 (0.90 to 1.76)	0.175
diabetes	1.80 (1.20 to 2.95)	0.02
LVEF imrpovement >20% after PCI	0.63 (0.42 to 0.94)	0.026
persistent high NFS>0.67 after PCI	1.52 (1.08 to 2.64)	0.033

Method: This is a nested case control study of the post PCI (percutaneous coronary intervention) registry from single tertiary hospital. Among 5589 patients who underwent PCI from 2010 through 2014, previously diagnosed 1510 NAFLD patients and 296 consecutive NAFLD patients who had undergone both PCI and ultrasonography of abdomen within 1 year between the tests were enrolled. (median age, 64 y (IQR 55–73)). We applied the NFS to the patients at baseline, using validated NFS cut-offs and 201 patients with higher NFS, defined as NFS > 0.67 at PCI, were 1:1 matched with controls, based on propensity scores for higher NFS > 0.67.
Results: Higher NFS (NFS > 0.67) was more prevalent in patients with left ventricle (LV) dysfuction (LV ejection fraction at PCI < 40%) than in those without (81.0% vs 33.6%, $p < 0.001$). Baseline higher NFS was

significantly associated with left ventricle dysfunction (adjusted OR 1.86, 95% CI 1.36 to 2.55, p < 0.001), and baseline higher NFS and persistent higher NFS at 1 year after PCI were independent predictor of a 5-years cardiovascular mortality, after adjustment for ejection fraction of left ventricle (adjusted HR 1.42, 95% CI 1.03 to 1.95, p = 0.023; adjusted HR 1.52, 95% CI 1.08 to 2.64, p = 0.033).



Conclusion: In this cohort study with a longitudinal assessment of the association between NAFLD status by NFS and the risk of cardiovascular mortality, we found post-PCI patients with persistent higher NFS were at higher risk of cardiovascular death compared with those without. An effort to reduce NFS could improve the long-term survival of post PCI patients, and NFS accurately identifies a unique group of post-PCI patients with significantly increased cardiovascular risk.

THU004

The association between liver fibrosis and cognitive impairment in type 2 diabetes: a cross-sectional sub-study of the south London diabetes cohort

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Background and Aims: Type 2 diabetes (T2D) and fatty liver disease are respective risk factors for cognitive impairment, yet their comorbidity in relation to cognitive impairment is poorly studied. For the first time, we tested whether comorbid liver fibrosis is associated with cognitive impairment in people with T2D.
Method: The South London Diabetes (SOUL-D) cohort is a population-based, multi-ethnic cohort of 1735 people recruited at diagnosis of T2D from South London primary care centres between 2008–2012. Nine years after diagnosis of T2D, we recruited a subset of 101 people to undergo transient elastrography (Fibroscan) of the liver; significant (F2) fibrosis was estimated using a standard cut-off ≥ 7kPa. We assessed cognitive function using the Rey-Osterreith Complex Figure (ROCF) test, a neuropsychological assessment in which subjects reproduce a complicated line drawing under three conditions: 1) by copying; 2) by immediate recall without reference to the figure; and 3) by recall after a 30-minute delay. This assesses a range of cognitive domains including visuospatial ability, attention, concentration, executive function and visual memory. We used linear regression models to test the association between liver fibrosis and cognitive performance on each condition. Results were adjusted for demographic-, metabolic- and psychological confounders.
Results: Of 149 people invited, 101 (67.8%) consented. The mean age was 63.6 (10.0) years, mean HbA1c 60.0 (19.2) mmol/mol, mean BMI 31.0 (5.8) kg/m^2, mean T2D duration 9.0 (0.5) years, and 52 (51.5%) were female and 52 (51.5%) of non-white ethnicity. Twenty-seven patients (26.7%) had significant fibrosis. After adjustment for age, sex, ethnicity, current HbA1c, current body mass index and current depressive symptoms using the Patient Health Questionnaire-9, liver fibrosis was associated with impaired performance on the ROCF copy condition (β = −5.47 [95% CI −8.34 to −2.60], p < 0.001), ROCF immediate recall condition (β = −6.30 [95% CI −10.30 to −2.30], p = 0.003) and ROCF delayed recall condition (β = −4.51 [95% CI −8.27 to −0.74], p = 0.02).
Conclusion: In this primary care population with T2D, there is preliminary evidence of impaired cognitive performance across multiple domains in those with comorbid liver fibrosis. Longitudinal replication of these findings on a larger scale is needed, including the assessment of potentially modifiable targets such as insulin resistance.

THU005

A new vision of non-alcoholic fatty liver disease: a "cardiac" disease per se and a "vascular" disease only with hypertension

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is associated with an increased cardiovascular (CV) risk. However, it is still not clear whether NAFLD contributes independently to the development and progression of CV disease. This study aimed to assess the differences between NAFLD patients with or without hypertension (HT) and patients with HT but no NAFLD through markers of subclinical and clinical atherosclerosis, cardiac function and morphology and liver fibrosis.
Method: Eighty-seven participants (51,9 ± 9 y; males = 83,7%) were divided according to the presence of NAFLD and essential HT in three groups: only-NAFLD, only-HT and NAFLD+HT. Patients with BMI>35 and type II diabetes were excluded. Blood pressure (BP) measurement, carotid ultrasonography, echocardiography and transient elastography were performed. Carotid intima–media thickness (cIMT), Carotid Distensibility (CD) and Carotid-femoral pulse wave velocity (cf-PWV) were measured as markers of subclinical atherosclerosis and arterial stiffness.
Results: The prevalence of atherosclerotic plaques was significantly higher in NAFLD+HT group compared with only-NAFLD group (40% vs 5,7%; p < 0,001). Belonging to NAFLD+HT group, rather than other clinical variables, was independently associated with atherosclerotic plaques in stepwise multiple logistic regression analysis (beta ± SEM = 2.083 ± 0.958; p = 0,01; exp(B) = 15,88 [95%CI, 1,62–155,00]). No differences in cIMT, CD, cf-PWV, echocardiographic parameters and liver stiffness were found among the three groups; nevertheless, a significant prevalence of concentric cardiac remodeling (RWT>0,42) was detected in all groups (only-HT, NAFLD+HT and only-NAFLD group at 40,9%, 35,7% and 33,3%, respectively; p = not significant).

Conclusion: Overt atherosclerosis, rather than subclinical atherosclerosis and arterial stiffness, was more evident in NAFLD+HT patients. A surprising finding was the high prevalence of concentric cardiac remodelling in all groups, including in the only-NAFLD one, suggesting a possible direct involvement of NAFLD in cardiac structural changes. Therefore, the impact of NAFLD on vascular and cardiac structure could be different and partially dependent on the presence of HT.

THU006

NASH is emerging as a leading cause of hospitalisation for cirrhosis: results from a real-life, prospective, consecutive cohort

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Background and Aims: There are no prospective, real-life driven estimates of the burden of NASH within the most severe end of spectrum of chronic liver disease, i.e. patients (pts) hospitalized for cirrhosis care.
Methods: All consecutive pts hospitalized in the Liver Unit during a 3-month time period starting on February 11th 2019 were included. The reason for hospitalisation was noted as cirrhosis-related or non-cirrhotic. Cirrhosis-related was further dichotomized in NASH alone or mixed NASH-another cause (based on long-term exposure to diabetes or obesity) and non-NASH causes (controls). Disease severity at entry, 6-month survival, readmission rate, diagnostic/therapeutic procedures performed during hospitalisation were captured.
Results: 173 pts were hospitalized, 85 for cirrhosis and 88 for other reasons. Among cirrhotics, 28 (33%) were NASH-related (NASH alone in 11, mixed cause in 17) while 13 (15%) were HCV, 8 (9%) HBV, 19 (22%) alcohol and 17 (20%) other causes. Overall, 58% were admitted for clinical decompensation and 42% for diagnostic/therapeutic procedures; 35% were Child-Pugh B and 24% Child-Pugh C. In NASH-related cirrhotics median MELD was 10 [7–34] vs 14 [6–32] in controls. Decompensation was the primary reason for hospitalisation in 39% NASH-cirrhosis vs 67% in controls, p = 0.016. NASH-related cirrhotics were Child-Pugh B in 33% and C in 11%; they had ascites (21%), jaundice (18%), encephalopathy (14%), gastrointestinal bleeding (11%), sepsis (4%), and/or SBP (4%) within 48 h of admission. Median hospital stay duration was 6 (1–21) days in NASH-cirrhosis and 7 (1–43) days in controls. 6-month readmission rate was 37% and 39%, respectively. During hospitalization, NASH-cirrhotic pts had endoscopy, variceal band ligation, paracentesis and HCC therapeutic procedures in 10, 4, 6, and 6 pts, respectively. 6-month mortality was 14% for NASH-related cirrhosis and 32% for controls (p = 0.133). Data on hospitalization costs will be provided.
Conclusion: In this first prospective real-life attempt to study, in a tertiary care center, the disease burden of NASH among hospitalized pts, NASH-related cirrhosis was the most prevalent cause for cirrhosis hospitalisation. Despite slightly lesser severity at entry, these pts had a high 6-month mortality, and similar duration of hospital stay and readmission rate as non-NASH cirrhotics. NASH-related cirrhosis is becoming a leading cause of decompensated cirrhosis requiring hospitalisation.

THU007

The paradigm of the two faced Janus: NAFLD and cardiovascular disease. An integrated and multidisciplinary new model to approach outpatients affected by diabetes type 2 and NAFLD

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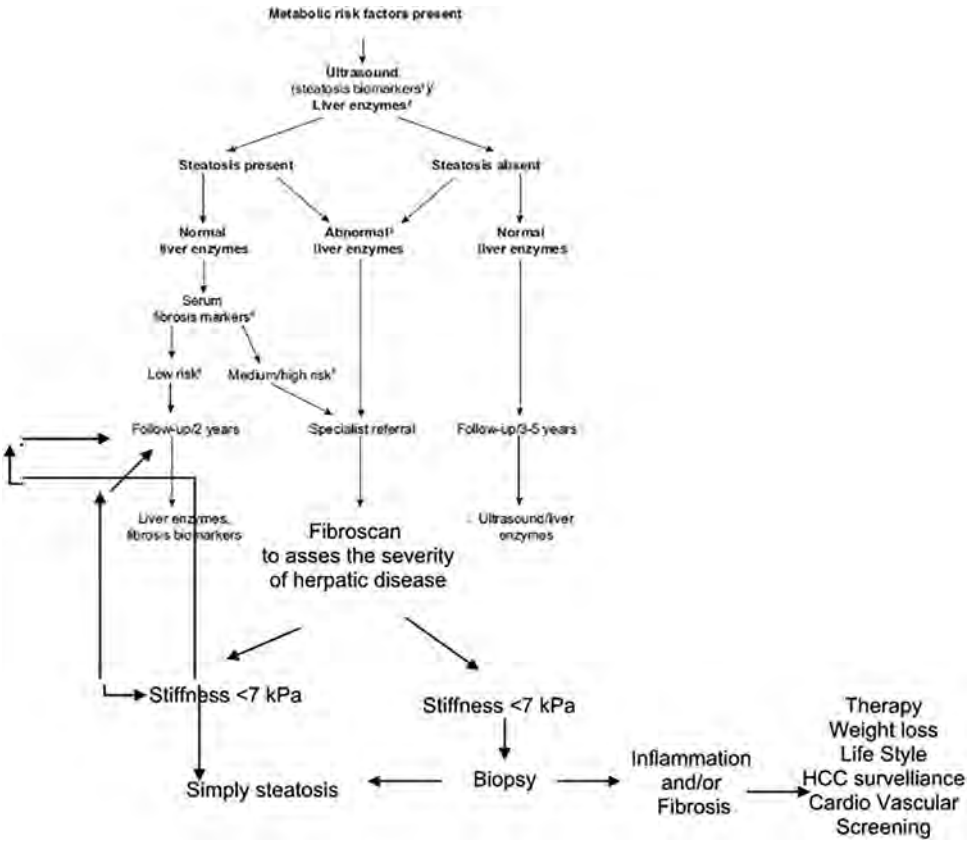

Figure: (abstract: THU007)

Background and Aims: Patients with NAFLD are at a higher risk of developing cardiovascular disease (CVD), infact CVD-related mortality is more common in patients with NAFLD in comparison to liver-related mortality. The aim of our study is to estimate the risk of CVD in adults DM2 patients with or without NAFLD. And also to present a new organizational model.
Method: We analyzed retrospectively a cohort of 6776 patients referraled from Diabetology Center of Padua that underwent to a regular follow up during the last two years. In collaboration to the Diabetologists and Cardiologists we start to evaluate the diabetic patients with suspicious of co-diagnosis of NAFLD trough the sequent algorithm (Fig. 1). In Day Service the patients perform: blood test with the elaboration of prognostic score: Fatty liver index, FIB-4 and Nafld fibrosis score, perform abdomen US and Fibroscan, Diabetologic and Hepatologic and Cardiological visit to asses the severity of disease. Patients with severe fibrosis (>7 kpa) underwent to Cardiovascular screening and recived medical therapies, life style suggestions, indication to lost weight and indication to follow up for surveliance for HCC.
Results: Among the 6776 diabetic patients, the incidence of NAFLD was 27.7% (NAFLD 1878 and NOT NAFLD 4898). NAFLD 1878 (M 1045 and F 833) and Cardiovascular Events in 560 (M 369 and F 191). NAFLD <65 years 803 (M 510 e F 293) and Cardiovascular Events in 213 (M152 and F 61). NOT NAFLD 4898 (M3027 and F 971) and Cardiovascular Events in 1305 (M940 and F465). NOT NAFLD <65 years 1324 (M889 and F435) and Cardiovascular Events in 256 (M191 and F65). CVD is dramatically associated to the diagnosis of diabetes type 2 (DM2) and also NAFLD in contrast to the esclusive diagnosis of DM2 and Not NAFLD ($p < 0.0001$ e Phi -0.09). CVD in patients >65 years is not different in NAFLD an NO NAFLD DM2 patients ($p = ns$). CVD in patients <65 years is significant associated to the diagnosis of NAFLD and DM2 (p0.0001 and Phi –0.08). Hepatocellular carcinoma is an anecdotal diagnosis in these patients in regular follow up and in treatment for diabetes.
Conclusion: Patients with NAFLD should be evaluated and managed accordingly in order to prevent further complications, in particular Cardiovascular Events. Possible management methods include innovative outpatients management with optimization of the time to asses the severity of disease and the subsequent right allocation of each case on specific follow up and indication.

THU009

Liver histopathology and extracellular matrix biomarkers in patients with advanced hepatic fibrosis from chronic hepatitis C who achieved a sustained virologic response

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Background and Aims: The use of direct-acting antivirals has made hepatitis C virus (HCV) eradication (sustained virologic response [SVR]) possible for most patients, including those with cirrhosis. SVR has been associated with regression of fibrosis; however, fibrosis persists in a substantial proportion of patients. Little is known about liver collagen content and the degree of fibrogenesis several years after SVR. Here, we describe baseline liver pathology, imaging, and circulating biomarkers of fibrosis in patients enrolled in study IM025-006 (NCT03420768) who had advanced hepatic fibrosis secondary to HCV and had achieved SVR at least 1 year prior to screening.
Method: Patients with METAVIR F3-F4 fibrosis were identified based on local pathologist assessment of liver biopsies obtained within 8 weeks of screening. Fibrosis was subsequently reassessed by a central pathologist. Patients with a history of chronic liver disease not due to HCV, decompensation, BMI over 34, and ALT level over 2× the upper limit of normal were excluded. Additionally, patients were originally required to have a platelet count above the lower limit of normal; this was amended to over 100 × 109/L toward the end of enrollment. Exploratory objectives included baseline assessments of histological biomarkers of collagen morphology and immunohistochemistry (collagen proportionate area [CPA] and alpha-smooth muscle actin [SMA]), liver stiffness imaging biomarkers (magnetic resonance elastography [MRE] and transient elastography [TE]), and circulating biomarkers of fibrosis and extracellular matrix remodeling (PRO-C3, C3M, TIMP-1, HA, PIIINP).
Results: Of 61 enrolled patients, 34 (56%) were men, mean (SD) age was 60.4 (7.5) years, and the median (Q1, Q3) time since SVR was 37.9 (23.8, 50.3) months. In these patients, mean (SD) platelet count was 197.2 (45.2) × 109/L. Based on central liver pathologist assessment, METAVIR scores were as follows: F1 (n = 8), F2 (n = 24), F3 (n = 19), and F4 (n = 10). Mean (SD) CPA and alpha-SMA were 3.3 (2.1) % and 4.3 (4.0) %, respectively. Mean (SD) MRE and TE were 3.7 (1.3) kPa and 10.9 (5.8) kPa, respectively. Mean (SD) PRO-C3 was 12.1 (3.7) ng/mL.
Conclusion: Findings suggest that, several years after SVR, patients with advanced hepatic fibrosis from HCV had low levels of hepatic collagen and liver stiffness and low levels of active fibrogenesis.

THU010

PNPLA3 gene polymorphism and overall and cardiovascular mortality among non-alcoholic fatty liver disease in the United States

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Background and Aims: The association between palatin-like phospholipase domain-containing 3 (*PNPLA3) I148M (rs738409)* polymorphism and mortality is not clearly understood. We determine the impact of *PNPLA3* polymorphism on overall and cardiovascular mortality among non-alcoholic fatty liver disease (NAFLD).
Method: The Third National Health and Nutrition Examination Survey (NHANES) from 1991 to 1994 and NHANES III-linked mortality data through 31 December 2015 were utilized. The primary outcome was the association between *PNPLA3* gene polymorphism and overall and cardiovascular mortality.
Results: NAFLD with *PNPLA3 GG* is more common in Hispanic, and had significantly higher liver chemistries and triglyceride than NAFLD with *PNPLA3 CC*. There was no association with overall or cardiovascular mortality among those with the *PNPLA3* G-allele. NAFLD with *PNPLA3* G-allele had lower overall mortality in age/sex-adjusted models (hazard ratio [HR] 0.57; 95% confidence interval [CI] 0.35–0.95). This association was marginally significant (HR 0.61 95% CI 0.37–1.00) adjusted with multiple metabolic risk factors include age, sex, race/ethnicity, smoking status, body mass index, presence of hypertension, presence of diabetes and total cholesterol. The *PNPLA3* G-allele was not associated with cardiovascular mortality.

Conclusion: *PNPLA3* polymorphism with G-allele in NAFLD was associated with lower overall mortality in a population-based US sample. While not statistically significant, the homozygous *PNPLA3* GG genotype showed a trend in decreased overall mortality in NAFLD.

	Age, sex -adjusted		Multivariable-adjusted	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Entire cohort (n=4,814)				
Overall mortality				
PNPLA3 CC (n=2441)	Reference		Reference	
PNPLA3 G-allele (n=2373)	0.90 (0.65-1.24)	0.493	0.90 (0.66-1.23)	0.499
PNPLA3 CG (n=1766)	0.87 (0.63-1.21)	0.386	0.88 (0.64-1.20)	0.388
PNPLA3 GG (n=607)	1.01 (0.57-1.76)	0.974	1.01 (0.57-1.79)	0.963
Cardiovascular mortality				
PNPLA3 CC (n=2441)	Reference		Reference	
PNPLA3 G-allele (n=2373)	0.99 (0.59-1.68)	0.979	0.96 (0.54-1.71)	0.887
PNPLA3 CG (n=1766)	0.87 (0.50-1.51)	0.594	0.84 (0.47-1.52)	0.551
PNPLA3 GG (n=607)	1.51 (0.50-4.57)	0.454	1.44 (0.43-4.79)	0.535
Among participants with NAFLD (n=1,952)				
Overall mortality				
PNPLA3 CC (n=886)	Reference		Reference	
PNPLA3 G-allele (n=1066)	0.57 (0.35-0.95)	0.034	0.61 (0.37-1.00)	0.051
PNPLA3 CG (n=755)	0.59 (0.34-1.04)	0.065	0.61 (0.34-1.09)	0.089
PNPLA3 GG (n=311)	0.52 (0.22-1.24)	0.134	0.61 (0.26-1.44)	0.249
Cardiovascular mortality				
PNPLA3 CC (n=886)	Reference		Reference	
PNPLA3 G-allele (n=1066)	0.71 (0.33-1.53)	0.366	0.75 (0.35-1.62)	0.445
PNPLA3 CG (n=755)	0.54 (0.17-1.74)	0.290	0.56 (0.17-1.79)	0.309
PNPLA3 GG (n=311)	1.29 (0.38-4.36)	0.666	1.53 (0.44-5.31)	0.488

Figure: (abstract: THU010): Associations between PNPLA3 Status and Overall Mortality and Cardiovascular Mortality

THU011

Renal failure is associated with increased mortality, morbidity, and hospital charges in patients admitted with non-alcoholic steatohepatitis

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Background and Aims: NASH is a common medical condition associated with significant morbidity and mortality. There exists a paucity of data regarding impact of kidney injury (defined as Acute and Chronic kidney injury) on outcomes of NASH hospitalizations. Our aim was to investigate the outcomes of hospitalized NASH patients with and without kidney failure.

Method: All patients ≥ 18 years old with NASH-related hospitalizations identified from National Inpatient Sample in 2016 were included in this study. NASH Patients with kidney failure were identified as cases and the control group was matched by using propensity scoring method. The scoring was based on a multivariate logistic regression model accounting for age, gender, race, primary insurance payer, hospital type, hospital bed size, hospital region, and hospital teaching status. Using 8-to-1-digit match, we paired each admission in kidney failure group with one admissions in non – kidney failure group.

Continuous variables were reported as means ± SD and categorical variables were reported as number and percentages. Paired Student's t-test was used to compare the difference of mean age between patients with and without NASH. *Wilcoxon rank-sum test were used for variables that are not normally distributed.* Rao-Scott modified chi-square test was used to test the difference of distribution for categorical variables.

Results: The overall sample included 7,135,090 patients. Among 6,855 patients admitted for NASH, 8.7% had comorbid kidney injury. NASH with renal failure patients were older (66 vs 55.1 years, p < 0.0001), had more comorbidities (CCI Score >3 71.9% vs 18.1%, p < 0.0001) (Elixhauser Score >4 80.6% vs 37.3%, p < 0.0001), and were Medicare insured (66.1% vs 31.4%, p < 0.0001). After adjusting for confounders through multivariate regression, patients in the renal failure group had markedly higher mortality (OR 38.72, CI 8.00–91.73), Length of Stay (OR 3.02 p < 0.0001), and total hospital charges (OR $37,045, p < 0.0001).

Table 2: Outcomes of NASH patients with and without Kidney Failure

	NASH with Kidney Failure	NASH without Kidney Failure	Multivariate Beta/OR (95% CI)	p-value
Mortality (n, %)	18 (3.0%)	1 (0.2%)	28.72 (8.99, 91.73)	<0.0001
Mean Length of stay, days (Mean, SD)	6.4 (9.1)	3.1 (3.4)	3.02 (2.54, 3.5)	<0.0001
Mean Total Charge of Hospitalization (Mean, SD)	78022.7 (158580.8)	38024.8 (33476.0)	37045.9 (31756.18, 42335.62)	<0.0001

*Results were adjusted for age, gender,CCI Score, Elixhauser Score, insurance tye, hospital region, hospital location/teaching status, and hospital bed size.

Conclusion: Prevalence of kidney injury in hospitalizations for NASH is associated with markedly increased mortality, morbidity, length of stay, and hospital costs. As a result, clinicians should be hypervigilant in treating kidney injury in this population. Further studies should continue to investigate further approaches for treatment.

THU012

Cardiovascular and cerebrovascular co-morbidities in non-alcoholic steatohepatitis

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Background and Aims: NASH is a chronic liver disease associated with insulin resistance and metabolic syndrome that has progressed

from simple steatosis. This study uses the Nationwide Inpatient Sample (NIS) 2016 with ICD-10 coding to demonstrate its link with cardiac and cerebrovascular comorbidities, as well as their impact on mortality, length of stay, and costs.

Method: All patients ≥ 18 years old with NASH-related in NIS 2016 were included in this study. Propensity scoring method was used to select the control group (patients without NASH). The comorbidities of NASH were identified within the NASH and non-NASH patients.

The univariate and multivariate logistic regression were used to estimate the odds ratio of having NASH for patients with the comorbidity after adjusting for patient demographics. In addition, the odds ratio of in-hospital mortality, beta estimate of average change in length of stay and hospital charges were estimated by using multivariate logistic regression model and multivariate linear regression, respectively. Statistical significance was defined by the two-sided test with a p-value <0.05.

Results: The cohort consisted of 7,135,090 patients. 6,855 patients with NASH were compared to 6,855 patients without NASH after propensity match. NASH was significantly associated with Cardiac and Cerebrovascular comorbidities after adjusting for confounding factors. Significant cardiac factors were ischemic heart disease, CHF, Afib, PVD, HTN, HLD, DM, TIA, Ischemic Stroke (Table 1). In terms of mortality, CHF, HLD, DM were significant predictors. CHF, Afib, HTN, HLD, DM were significant predictors of LOS. For total charges, Ischemic Heart disease, CHF, Afib, DM significantly increased hospitalization charges.

Table 1: Association of comorbidity and NASH status

	Adjusted*	Mortality	Length of Stay	Total Charge of Hospitalization
Comorbidity	OR (95% CI)	OR (95% CI)	Beta (95% CI)	Beta
Chronic Ischemic Heart Disease	1.99 (1.8, 2.19)	*	*	4452.57
CHF	7.19 (6.15, 8.4)	3.37 (1.11, 10.28)	2.36 (1.62, 3.11)	10971.68
Afib	3.15 (2.75, 3.61)	*	0.76 (0.17, 1.35)	7525.42
PVD	2.64 (2.1, 3.33)	*	*	*
HTN	1.12 (1.03, 1.2)	*	−0.49 (−0.76, −0.22)	−3086.64 (−6100.77, −72.51)
HLD	0.84 (0.78, 0.9)	0.21 (0.07, 0.62)	−0.55 (−0.82, −0.28)	*
DM	2.31 (2.07, 2.58)	2.76 (1.01, 7.52)	1.5 (1.03, 1.97)	21551.57 (16355.54, 26747.59)
TIA	2.63 (1.48, 4.68)	*	*	*
Ischemic Stroke	8.06 (4.03, 16.11)	*	*	*

*not significant.

Conclusion: In this study we demonstrate significant cardiac and neurologic risk factors of NASH that lead to advanced disease. We also demonstrate that they are linked to increased mortality, length of stay, and costs. Targeting these risk factors early would decrease morbidity and mortality in NASH and decrease hospital costs.

THU013

Extra-hepatic gastrointestinal malignancies in NAFLD: nationwide inpatient sample 2016

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Background and Aims: Malignancy is a common cause of mortality NAFLD. In this study we seek to examine extrahepatic gastrointestinal malignancies in NAFLD. We used the Nationwide Inpatient Sample (NIS 2016).

Method: All patients ≥ 18 years old with and without NAFLD in NIS 2016 were included. Propensity scoring method was used to select the control group (patients without NAFLD). Malignancies were identified within the NAFLD and non-NAFLD patients. NAFLD was defined as Fatty Liver (ICD 10 K76.0) and NASH (ICD 10 K 75.81). Esophageal malignancy (ICD10 C15.9), gastric malignancy (ICD 10C16.9), large intestinal malignancy (ICD 10 C18.9) were used.

The univariate and multivariate logistic regression were used to estimate the odds ratio of having NAFLD after adjusting for patient demographics. In addition, the odds ratio of in-hospital mortality, beta estimate of average change in length of stay and hospital charges were estimated by using multivariate logistic regression model and multivariate linear regression, respectively. Statistical significance was defined by the two-sided test with a p-value <0.05.

Results: The study sample consisted of 7,135,090 patients. 6,855 NAFLD patients were matched with 6,855 non-NAFLD patients. Esophageal malignancy was found in .2%, gastric malignancy in .3%, large intestinal malignancy in .9%. Esophageal and gastric malignancies were significantly correlated with NAFLD on multivariate logistic regression analysis. Esophageal malignancy, OR 6.98 (95% CI 1.59, 30.7), Gastric Malignancy, OR 5.55 (95% CI 1.91–16.13). Malignancy of large intestine was not significantly correlated on univariate or multivariate analysis, OR .83 (95% CI .57–1.21). No significant correlation of length of stay, mortality, or hospital costs was seen with malignancy.

	Patients with NAFLD (n = 6855)	Patients without NAFLD (n = 6855)	Crude OR		Adjusted OR	
Malignancy			OR (95% CI)	p-value	OR (95% CI)	p-value
Esophageal Cancer	14 (0.2%)	2 (0.0%)	7 (1.59, 30.8)	0.0100	6.98 (1.59, 30.7)	0.0102
Gastric Cancer	22 (0.3%)	4 (0.1%)	5.51 (1.9, 16)	0.0017	5.55 (1.91, 16.13)	0.0016
Large Intestinal cancer	50 (0.7%)	60 (0.9%)	0.83 (0.57, 1.21)	0.3404	0.83 (0.57, 1.21)	0.3292

Conclusion: We demonstrate a significant link between esophageal and gastric malignancy in NAFLD. Previous studies have shown an increased risk of HCC, colorectal, and breast cancer. Obesity is thought to be the primary driver, but insulin resistance and metabolic syndrome may also contribute. Further studies are needed to stratify specific cancer subtypes.

THU016

Prevalence of non-alcoholic fatty liver in the Netherlands: the Netherlands Epidemiology of Obesity study

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Background and Aims: Non-alcoholic liver disease (NAFLD), defined as a hepatic triglyceride content of more than 5.56% not due to excessive alcohol consumption. NAFLD covers a wide clinical spectrum, ranging from steatosis to non-alcoholic steatohepatitis, and increases the risk of end-stage liver disease and mortality. It is strongly associated with obesity, and with increased risks of type 2 diabetes, and cardiovascular diseases. Recent studies suggest an increased prevalence of NAFLD in Europe, but the prevalence of NAFLD in The Netherlands is currently unknown. We aim to determine the overall prevalence of NAFLD in a large Dutch population-based study, and in different subgroups with well-known risk factors of NAFLD.
Method: The Netherlands Epidemiology of Obesity (NEO) study is a population-based prospective cohort study in 6671 participants. Participants completed several questionnaires and underwent an extensive physical examination including blood sampling. Hepatic triglycerides content was assessed using proton magnetic resonance spectroscopy in a random subgroup of 2083 participants.
Results: Mean age of the population was 55.5 years, mean BMI 25.8 kg/m^2 and 47% were men. The prevalence of steatosis was 27%. The prevalence of steatosis was increased in elderly (55–65 years) participants (33%), men (36%), participants with a BMI >30 kg/m^2 (63%), diabetes (72%) and PNPLA3 CG and GG allele polymorphism (33%). Steatosis prevalence was even higher in subgroups with combined risk factors, e.g. in participants who had combined presence of high triglycerides and impaired glucose metabolism the prevalence of steatosis was 93%. Although less frequent, steatosis was also present in 13% of participants without overweight.
Conclusion: This study shows that hepatic steatosis, as assessed by proton magnetic resonance spectroscopy, is present in over a quarter of the general population in The Netherlands. The prevalence is higher is subgroups with well-known risk factors for NAFLD and especially if more than one risk factor is present.

THU017

Association between non-alcoholic fatty liver disease and nut consumption

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Background and Aims: Nut consumption has been associated with reduced inflammation, insulin resistance, and oxidative stress. Therefore, we aimed to investigate the influence of nut consumption on prevalence and severity of NAFLD and the metabolic syndrome.
Method: 1362 asymptomatic subjects were included as part of a colorectal carcinoma colonoscopy screening program (SAKKOPI). Patients were characterized using biochemical and metabolic parameters and food frequency questionnaire. The diagnosis of NAFLD was established by transient elastography-based controlled attenuation parameter (CAP) >248 dB/m after exclusion of other liver diseases, excess alcohol consumption and viral hepatitis. Steatosis was graded as >248/>268/>280 dB/m for any, moderate and severe steatosis. Significant fibrosis was defined by a liver stiffness ≥ 8 kPa. Consumption of nuts was graded as: no consumption or <1 time/week; 1–3 times/week; 1 time/day and ≥ 2 times/day.
Results: Mean age was 58.7 ± 8.7years with a mean BMI of 26.7 ± 4.7 and a 28.3% prevalence (n = 394) of diabetes. Mean CAP value was 257 ± 75 dB/m with 707 patients (56.4%) having NAFLD. Median liver stiffness was 4.5 (interquartile range [IQR]:3.7–5.7)kPa while 94 patients (7.5%) had significant fibrosis. When comparing patients with and without daily nut intake, significant differences were observed for BMI (27.0 ± 4.7 vs 25.2 ± 4.2, p < 0.001), prevalence of diabetes (335 [29.7%] vs 45 [19.2%], p = 0.001), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR; 1.63 [0.90–2.36] vs 1.33 [0.82–1.84], p < 0.001), triglycerides (101 [68–134] vs 89 [63–115]mg/dl, p = 0.001) and ALT (21 [14–28] vs 19 [13–24]U/l, p = 0.001) as well as liver stiffness (4.6 [3.6–5.6] vs 4.2 [3.3–5.1]kPa, p < 0.001) and CAP value (261 ± 75 vs 239 ± 73 dB/m p < 0.001). Moreover, distribution of steatosis stages was significantly different with 426 (41.1%) vs 59 (27.2%) showing severe steatosis (p < 0.001). A consecutive decrease among subgroups of nut consumption was observed for liver stiffness (4.6 [3.8–5.8] vs 4.6 [3.7–5.8] vs 4.2 [3.4–5.2] vs 4.1 [3.3–5.2], p < 0.001), CAP (264 ± 76 vs 257 ± 73 vs 239 ± 72 vs 240 ± 80 dB/m, p = 0.001), BMI (27.4 ± 4.9 vs 26.5 ± 4.5 vs 25.1 ± 4.1 vs 25.4 ± 4.5, p < 0.001) and HOMA-IR (1.72 [1.11–2.62] vs 1.53 [1.02–2.42] vs 1.37 [0.92–2.08] vs 1.31 [0.78–1.59], p < 0.001).
On multivariate binary logistic regression analysis investigating factors independently associated with the presence of hepatic steatosis, nut intake (odds ratio [OR]: 0.854 [95% confidence interval (CI): 0.733–0.995], p = 0.044) was significantly associated with hepatic steatosis correcting for BMI, age, HOMA-IR, liver stiffness and low/moderate alcohol intake.
Conclusion: Nut intake is inversely associated with hepatic steatosis and shows a trend towards less liver fibrosis. Additionally, nut consumption shows beneficial effects on other factors of the metabolic syndrome.

THU018

Myosteatosis and sarcopenia are prevalent in patients with NAFLD even in the absence of advanced fibrosis

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Background and Aims: Muscle fat infiltration, termed myosteatosis, is reported in patients with NAFLD, however its prevalence in non-cirrhotic patients is unknown. The same is true for sarcopenia and sarcopenic obesity. We analysed the presence of sarcopenia and fat infiltration in the muscular mass in a cohort of NAFLD patients with different disease severity.
Method: Patients with NAFLD and different stages of liver fibrosis who underwent a CT scan for any reason within 365 days from a liver biopsy or transient elastography with Fibroscan were included and divided into groups of mild-moderate (F0-F2) and advanced fibrosis (F3-F4). We also included patients with decompensated NASH cirrhosis who had a CT scan performed during the assessment for liver transplantation. Cross-sectional area index (CSMI), erector spinae fat-free muscle area (FFMA) and attenuation indexes measured at L3 level section of the CT scan were used to measure the muscle mass and presence of fat infiltration in muscles. Sarcopenia$^{L3\text{-}CSMI}$ was defined as L3-CSMI below 39 cm^2/m^2 in women and 50 cm^2/m^2 in men and myosteatosis was defined as <41HU in patients with a BMI up to 24.9, and <33 in those with a BMI ≥ 25 kg/m^2.
Results: We included 149 patients, 38.3% females, mean age 57.8 ± 10.5 years, BMI 31.7 ± 6.1 kg/m^2. Population was divided in F0-F2 n = 63 (42%), F3-F4 n = 43 (29%) and F4 decompensated (F4d) n = 43 (29%). Patients with sarcopenia were equally distributed in all fibrosis stages: F0-F2 21%, F3-F4 21% and F4d 28% (p = 0.64) despite a mean BMI >25 kg/m^2.
The fatty tissue infiltration of the erector spinae was 15% of the total muscular area and the proportion was equal throughout the groups. Eighty-nine patients (60%) had myosteatosis: 43 (48%) in F0-F2, 24 (27%) in F3-F4 and 22 (25%) in F4d (p = 0.175). Comparing patients with and without myosteatosis, CSMI was significantly higher in the myosteatosis group in F0-F2 and F3-F4 (by 10 cm2/m2 in both groups,

p < 0.001 and p = 0.003, respectively), but not in F4d CSMI. No predictors of sarcopenia were found in multivariable analysis.
Conclusion: A significant proportion of patients with NAFLD have sarcopenia, even in the absence of advanced fibrosis. Fat infiltration defined as fatty area of ES and myosteatosis, might confound the definition of sarcopenia leading to underestimation of its true prevalence. Therefore, further studies with larger populations are needed to define validated sarcopenia cut-off values for these patients.

THU019

A cholestatic pattern predicts liver outcomes in patients with non-alcoholic fatty liver disease

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Background and Aims: The expression of NAFLD (non-alcoholic fatty liver disease) in liver biochemistry has usually a "cytolitic" pattern (raised ALT, normal ALP), but a "cholestatic" pattern (low ALT, raised ALP), can also be observed. We aimed to assess the prevalence of the "cholestatic" pattern in subjects with NAFLD at different stage of fibrosis and its impact on development of liver events and death.
Method: A cohort of consecutive NAFLD patients diagnosed by biopsy or, in the case of patients with compensated cirrhosis, by transient elastography and/or evidence of portal hypertension. Patients were divided into 3 groups based on the pattern of elevated liver enzymes as follows: predominantly cholestatic pattern (C pattern), predominantly hepatocellular pattern (H pattern), and mixed (M) pattern by using the formula (ALT/ALTULN)/(ALP/ALPULN). C pattern group included patients with a ratio of less than 2, whereas the H pattern group included patients with a ratio of more than 5. The M pattern group consisted of patients with a ratio between 2 and 5. Liver outcomes (decompensation –ascites, encephalopathy, variceal bleeding, jaundice- and hepatocellular carcinoma, HCC), as well as total and liver deaths were recorded during follow-up.
Results: 529 patients (62.4% males, mean age 49.8 years, mean BMI 30.3 Kg/m2, 46% with diabetes, 34.8% with F3-F4 fibrosis, 21.4% with cirrhosis) with a mean follow-up time of 68.3 months were enrolled. H, M and C patterns were found in 159 (30.1%), 258 (48.8%) and 112 (21.1%) patients, respectively. The prevalence of the C pattern was significantly higher in patients with cirrhosis when compared to all the other (17.7% in F0-F1, 8.4% in F2, 12.7% in F3 and 46% in cirrhosis, respectively, p < 0.001). 27 (5.1%) hepatic decompensation, 16 (3%) HCC, 17 (3.2%) total deaths and 14 (2.6%) and liver deaths were recorded, all occurring in patients with F3-F4 fibrosis. In the entire cohort, at multivariate Cox regression analysis adjusted for age, IFG/diabetes (not for overall mortality), PLT, albumin and F3-F4 fibrosis, C versus M versus H pattern was independently associated with a higher risk of hepatic decompensation (HR 2.42, 95% C.I. 1.02–5.74, p = 0.04), HCC (HR 2.90, 95% C.I. 1.01–8.34, p = 0.04), and liver deaths (HR 3.98, 95% C.I. 1.09–14.4, p = 0.03). Comparable results were observed in patients with F3-F4 fibrosis for liver decompensation (HR 2.63, 95% C.I. 1.11–6.23, p = 0.02), HCC (HR 2.94, 95% C.I. 1.03–8.41, p = 0.04), and liver deaths (HR 3.98, 95% C.I. 1.09–14.4, p = 0.03).
Conclusion: Patients with NAFLD cirrhosis have frequently a cholestatic pattern This is associated to a higher risk of decompensation, HCC and liver death.

THU020

Impact of non-alcoholic fatty liver disease on cardiovascular risk in a general population

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Background and Aims: Non-alcoholic fatty liver (NAFL) is a major cause of liver disease worldwide leading also to a higher risk of cardiovascular events. We aimed to evaluate the impact of fatty liver and fibrosis on cardiovascular risk in a general population.
Method: 542 subjects included in the community-based ABCD (Alimentazione, Benessere Cardiovascolare e Diabete) study were recruited. Steatosis (CAP >288 dB/m) and severe fibrosis (Low risk, LSM <7.9 KPa with M probe and <5.7 KP with XL probe; intermediate risk, LSM 7.9–9.5 KPa with M probe and 5.7–9.2 KPa with XL probe; high risk, LSM ≥ 9.6 KPa with M probe and ≥ 9.3 KPa with XL probe) were assessed with FibroScan. Intima-media thickness (IMT) was measured with ultrasound (US). Multivariate linear, ordinal and logistic regression analyses were used to identify predictors of CV risk and IMT. Cardiovascular risk was evaluated by the Atherosclerotic Cardiovascular Disease (ASCVD) risk estimator and defined low if <5%, borderline if 5%–7.4%, intermediate if 7.5%–19.9% and high if ≥ 20%.
Results: Prevalence of steatosis and of severe fibrosis in this cohort were 31.7% and 6.8%, respectively. Subjects with NAFL, when compared to those without did not differ for IMT (0.75 vs 0.72 mm; p = 0.11) and IMT ≥ 1 mm (15.6% vs 12.1%; p = 0.24). Patients with high versus intermediate and low risk of severe fibrosis had a trend for higher IMT (0.72 ± 0.21 vs 0.79 ± 0.19 vs 0.79 ± 0.21 mm respectively; p = 0.08) and significant higher prevalence of IMT ≥ 1 mm (12.1% vs 28.6% vs 24% respectively; p = 0.03) and these association were maintained after adjusting for confounders (p = 0.04 for IMT; OR 2.73,95%C.I. 1.03–2.89, p = 0.03 for IMT ≥ 1 mm). ASCVD score was evaluated in patients with and without steatosis (Table 1) and according to the risk of severe fibrosis (Table 2). Notably, by ordinal regression analysis, both steatosis (OR 1.74, 95% C.I. 1.22–2.50, p = 0.002) and high versus intermediate and low risk of severe fibrosis (OR 1.78, 95% C.I.1.26-2.50, p = 0.001) were independent risk factors for a higher ASCVD risk after adjusting for obesity.

Table 1: Evaluation of ASCVD score in subjects with and without steatosis

	ATHEROSCLEROTIC CARDIOVASCULAR DISEASE SCORE (ASCVD)				
	Low	Borderline	Intermediate	High	p value
Steatosis (%)	30.3	11	30.3	28.4	<0.001
No steatosis (%)	49.4	10.5	20.5	19.6	

Table 2: Evaluation of ASCVD score in subjects with low, intermediate and high risk of fibrosis

	ATHEROSCLEROTIC CARDIOVASCULAR DISEASE SCORE (ASCVD)				
	Low	Borderline	Intermediate	High	p value
Low risk of fibrosis (%)	46	8.3	23.2	20.5	<0.001
Intermediate risk of fibrosis (%)	20.7	24.1	27.6	27.6	
High risk of fibrosis (%)	19.2	3.9	26.9	50	

Conclusion: In the setting of a general adult population the presence of NAFL and of severe fibrosis is linked to a high rate of cardiovascular risk factors, pointing towards the need for specific preventive measures.

THU021

Serum zinc level and liver fibrosis in male patients with non-alcoholic fatty liver disease

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Background and Aims: The role of zinc in non-alcoholic fatty liver disease (NAFLD) is not clear. This study aimed to investigate the relationship between serum zinc level and liver fibrosis in patients with NAFLD.
Method: A cross-sectional study was conducted using nationally representative samples from the Korean National Health and Nutrition Examination Survey 2010. A total of 658 male adults were enrolled in the study. Liver fibrosis was assessed using Fibrosis-4 (FIB-4) index. The significant liver fibrosis was defined as FIB-4 index was more than 1.3. Zinc was measured using inductively coupled plasma mass spectrometry using PerkinElmer ICP-MS (PerkinElmer, MA, USA). Pearson correlation analysis was used to evaluate the relationship between serum zinc level and FIB-4 index. Univariable and multivariable logistic regression analyses were done to assess the risk factors including serum zinc level for significant liver fibrosis in patients with NAFLD.
Results: Of 658 male adults, a total of 197 patients with NAFLD were finally analyzed. The mean level of serum zinc was 144.3 ± 30.3 μg/dL. FIB-4 index was significantly increased as the serum zinc level decreased (Pearson correlation coefficient = –0.166, $p = 0.019$). The significant liver fibrosis (FIB-4 index ≥ 1.3) was observed in 48 patients (24%). The multivariable analysis showed that the significant liver fibrosis in patients with NAFLD was associated with age ≥ 50 years (hazard ratio [HR] 9.22 with 95% confidence interval [CI]: 3.54–24.51, $p < 0.001$), serum zinc level <140 μg/dL (HR 3.05 with 95% CI: 1.38–6.79, $p = 0.006$), and diabetes mellitus (HR 2.43 with 95% CI: 1.09–5.41, $p = 0.033$).
Conclusion: There was an inverse relationship between serum zinc level and FIB-4 index in patients with NAFLD. Low level of serum zinc was an independent risk factor for significant liver fibrosis in NAFLD. Further studies are needed to clarity the effect of zinc on liver fibrosis in NAFLD.

THU022

Identification of factors associated with engagement and adherence to a very low calorie diet to achieve significant weight loss in patients with advanced non-alcoholic fatty liver disease: a qualitative evaluation

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is associated with excessive calorie consumption, insufficient physical activity and subsequent obesity. The recommended therapy for NAFLD is lifestyle modification to achieve weight-loss. Patients with advanced NAFLD may not have been successful in engaging with, or have undertaken, lifestyle interventions to initiate weight-loss. This qualitative study aimed to identify factors associated with engagement and adherence of patients with advanced NAFLD to an 8–12 week very low calorie diet (VLCD).
Method: 30 patients with advanced NAFLD were recruited to an 8–12 week VLCD (~800 kcal/day), using meal replacement products (Optifast, Nestlè Health Science). Following completion of the VLCD intervention, patients took part in a semi-structured face-to-face interview. Interviews were audio recorded, transcribed verbatim and thematically analysed to identify common themes associated with uptake and adherence.
Results: 27/30 patients completed the VLCD and 23 took part in an interview. The VLCD was reported by patients as an acceptable and feasible method of achieving significant weight loss to achieve improved liver health. The primary motivator for uptake was a "desire to achieve rapid weight loss (3–39 kg) to improve liver and diabetes-related health"; a significant factor to continued engagement was "accountability to the healthcare professionals providing support and guidance"; key facilitators to adherence were "ease of following the VLCD," "regular visits with feedback and praise from a medical professional" and "practical and emotional support from friends, colleagues and family members." Motivation, and subsequent adherence, was maintained by early weight-loss. Perceived barriers were highly individual, however "shift work" was commonly reported by those who struggled to adhere.
Conclusion: Findings suggest that use of the VLCD as a management option for NAFLD relies on frequent visits to clinic, personalised feedback provision, practical and social support, positive reinforcing feedback from healthcare professionals and practical and emotional support from friends, colleagues and family members. Moreover, early weight loss mediated intervention completion.

THU023

Lack of histological steatohepatitis features in advanced fibrosis could impact in screening failure rate: a comparison with FDA clinical criteria

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Background and Aims: Rates of screening failure in NAFLD randomized clinical trials (RCT) are unacceptably high, being the lack of a complete histological definition of NASH one of the leading causes in patients with advanced fibrosis and cirrhosis. FDA allows including patients with one metabolic risk factor, ALT>40 IU/mL and F > 1 by elastography in the absence of liver biopsy in early RCT (Siddiqui, Hepatology 2018). We assessed the prevalence of histological steatohepatitis features in patients with advanced fibrosis and cirrhosis.

Method: Spanish multicenter study including 2249 biopsy-proven NAFLD patients from HEPAmet registry. NASH was diagnosed by NAS and SAF scores (including steatosis, ballooning, and lobular inflammation), and fibrosis by Kleiner score.

Results: Fibrosis was: F0 38.2% (858/2249), F1 26.1% (588/2249), F2 15% (337/2249), F3 13.7% (307/2249) and F4 7.1% (159/2249). NASH was: NAS 44.2% (994/2249) and SAF score 49.6% (1116/2249). Table shows percentage of steatosis, ballooning, lobular inflammation, and NASH across the fibrosis stages. According to NAS, 57.3% (267/466) of F3 and 45.9% (73/159) of F4 patients would have NASH, while these percentages would be F3 61.1% (285/466) and F4 52.8% (84/159) using SAF score (p = ns). Defining NASH by the presence of one of NAS or SAF score, it would be F3 67.8% (316/466) (p = 0.03) and F4 58.5% (93/159) (p = 0.02). Taking into account FDA criteria (at least, one metabolic factor together with ALT>40 IU/mL), the percentage of NASH would increase to F3 81.1% (378/466) and F4 74.2% (118/159) (p < 0.0001 over NAS and SAF for both F3 and F4).

Steatosis*						
	F0	F1	F2	F3	F4	P value
Patients (%)	75.6	86.9	92.6	92.5	86.2	<0.0001
Ballooning*						
	F0	F1	F2	F3	F4	P value
Patients (%)	43.7	70.7	78.9	76.5	63.5	<0.0001
Lobular inflammation*						
	F0	F1	F2	F3	F4	P value
Patients (%)	50.7	77.6	87.5	85.3	76.7	<0.0001
NAS score*						
	F0	F1	F2	F3	F4	P value
Mean ± SD	2.4 ± 1.7	3.5 ± 1.7	4.2 ± 1.7	3.9 ± 1.5	3.4 ± 1.7	<0.0001
NASH (NAS score ≥ 4)*						
	F0	F1	F2	F3	F4	P value
Patients (%)	25.8	49.1	64.4	63.2	45.9	<0.0001
NASH (SAF score)*						
	F0	F1	F2	F3	F4	P value
Patients (%)	31	56.5	69.1	65.5	52.8	<0.0001

*p < 0.05 between F4 *versus* F3 and F2.

Conclusion: Steatohepatitis histological criteria disappeared progressively with the fibrosis stage, so about half of the patients could be screening failure in RCT. To add NAFLD-related clinical criteria (such as metabolic risk factors and ALT) to the uncomplete NASH histological diagnosis in advanced fibrosis and/or cirrhosis could benefit patients whose main aim is to prevent cirrhosis complications, liver transplant, and death.

THU024

Risk factors associated to NAFLD-related advanced fibrosis in patients with normal ALT levels

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Background and Aims: The risk of advanced NAFLD in subjects with ALT<40 IU/mL is unclear. We aimed to know the prevalence and risk factors of NAFLD-related advanced fibrosis in patients with strictly normal transaminase levels.

Method: Spanish multicenter study including 2414 biopsy-proven NAFLD patients from HEPAmet registry. Definition of strictly normal ALT: male sex <30 IU/mL; female sex <19 IU/mL. Advanced fibrosis was F3-F4 *vs.* F0-F2.

Results: The 46.4% (1121/2414) of patients showed NASH and 20% (482/2414) advanced fibrosis. AST increased progressively across fibrosis stages (F0 36 ± 46; F1 39 ± 29; F2 47 ± 37; F3 50 ± 31; F4 55 ± 43 IU/mL; p < 0.0001), while ALT increased from F0 to F2 and decreased in F3 and F4 (F0 54 ± 59; F1 58 ± 47; F2 66 ± 59; F3 63 ± 43; F4 58 ± 73 IU/mL; p = 0.005). Normal ALT levels were shown in 20% patients (482/2414), and they showed a lower percentage of NASH (36.6% (160/437) *vs.* 51.8% (954/1841); p < 0.0001) and advanced fibrosis (14.8% (68/458) *vs.* 22% (408/1855); p = 0.001), but not cirrhosis (5.9% (27/458) *vs.* 7.4% (137/1855); p = 0.266). Age

[OR 1.04 (IC95% 1.01–1.08); p = 0.016], diabetes [OR 3.08 (IC95% 1.49–6.39); p = 0.002], platelets [OR 0.98 (IC95% 0.98–0.99); p = 0.0001], AST [OR 1.10 (IC95% 1.04–1.16); p = 0.001], and GGT [OR 1.01 (IC95% 1.00–1.01); p = 0.015] were associated with advanced fibrosis in presence of normal ALT (Table). ROC analysis was 0.89 (IC95% 0.85–0.93; p < 0.0001) and the best cut-off (Se 81.5%, Sp 83.1%; NPV 96.1%, PPV 46.9%; LR+ 4.82, LR- 0.22) separated adequately the risk of advanced fibrosis (46.9% (53/113) *vs.* 3.9% (12/307); p < 0.0001).

Characteristic	Unadjusted OR (95%CI) Advanced Fibrosis	Adjusted OR (95%CI) Advanced Fibrosis
Male sex	2.53 (1.46–4.40); p = 0.001	
Age; years ± SD	1.07 (1.04–1.10); p = 0.0001	1.04 (1.01–1.08); p = 0.016
BMI ± SD (kg/m^2)	0.95 (0.92–0.98); p = 0.002	
Arterial Hypertension	1.77 (1.05–3.00); p = 0.033	
Type 2 diabetes mellitus	4.88 (2.84–8.38); p = 0.0001	3.08 (1.49–6.39); p = 0.002
Glucose ± SD (mg/dL)	1.01 (1.00–1.02); p = 0.002	
Total cholesterol ± SD (mg/dL)	0.99 (0.99–1.00); p = 0.013	
Triglycerides ± SD (mg/dL)	1.00 (1.00–1.00); p = 0.888	
Hypertriglyceridemia	1.54 (0.92–2.60); p = 0.104	
Albumin ± SD (g/dL)	0.71 (0.39–1.31); p = 0.279	
Bilirubin ± SD (mg/dL)	1.96 (1.03–3.73); p = 0.039	
Platelet count ± SD (×10^9/L)	0.98 (0.98–0.99); p = 0.0001	0.98 (0.98–0.99); p = 0.0001
AST ± SD (IU/mL)	1.15 (1.11–1.21); p = 0.0001	1.10 (1.04–1.16); p = 0.001
ALT ± SD (IU/mL)	1.09 (1.04–1.14); p = 0.001	
GGT ± SD (IU/mL)	1.01 (1.01–1.02); p = 0.0001	1.01 (1.00–1.01); p = 0.015
Transient elastography (kPa)	1.08 (1.03–1.15); p = 0.005	

Conclusion: ALT had not good predicting accuracy for NAFLD severity since it decreased in advanced fibrosis in a U-shaped relationship. Age, diabetes, AST, GGT, and platelets were essential to detect patients with advanced fibrosis in patients with strictly normal ALT levels.

THU025

Fibrosis quantification by image morphometry of liver fibrosis predicts clinical outcomes in patients with non-alcoholic fatty liver disease

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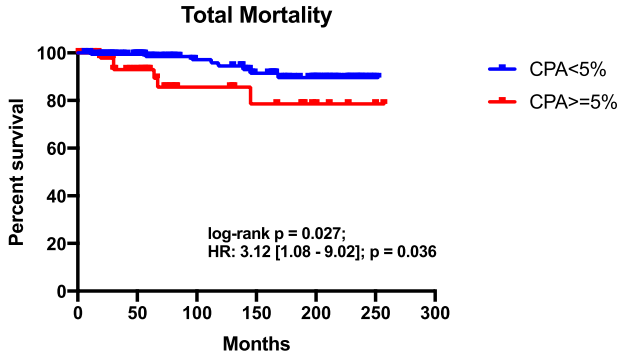
Background and Aims: Liver fibrosis predicts adverse clinical outcomes such as decompensation and liver-related death (LRD) in patients with nonalcoholic fatty liver disease (NAFLD). Pathologist staging of liver biopsy is the current gold-standard however it may suffer from observer variability. We aimed to investigate the accuracy of the collagen proportionate area (CPA) as an objective and reproducible method of predicting adverse outcomes in patients with NAFLD.
Method: Patients who attended a tertiary centre Hepatology Department from 1992 to 2015 with biopsy proven NAFLD were included. Computerized image morphometry was performed on biopsy slides stained by Sirius Red with CPA analyses performed by ImageScope v12.3.3. Fibrosis was staged according to the NASH-CRN scoring system. Clinical outcomes were determined by medical records and population-based data-linkage. Statistical analyses were performed by SPSS.
Results: A total of 208 patients (47% male, mean age 49 years) were followed for a median (interquartile range, IQR) of 6.0 (4.0–15.0) years totalling 1801 person-years. Death or liver transplantation occurred in 14 patients among which 5 had LRD and 7 patients developed liver decompensation. The median CPA value at baseline biopsy was 3.09% (IQR: 1.72–4.99%). CPA correlated significantly with pathologist fibrosis stage (Spearman rho 0.479, p < 0.001). Patients with higher CPA (> = 5.00%) had higher risks for total mortality [hazard ratio (HR): 3.12 (1.08–9.02); p = 0.036], liver related death [HR 14.48 (1.62–129.67); p = 0.017], and liver decompensation [HR 9.22 (1.79–47.63); p = 0.008]. CPA and pathologist fibrosis staging (FS) showed similar accuracy (AUROC) for the prediction of outcomes; total mortality, CPA: 0.623 (95% CI: 0.446–0.799), FS: 0.676 (0.509–0.837); LRD, CPA: 0.872 (0.691–1.000), FS: 0.917 (0.788–1.000); decompensation, CPA: 0.774 (0.555–0.993), FS: 0.823 (0.621–1.000); all p > 0.05]. In the sub-group of patients with cirrhosis (n = 9), a CPA cut-off of 10.0% was able to further stratify patients with higher and lower future risk of death or liver transplant (86% vs. 0%), LRD (86% vs. 0%), and decompensation (86% vs. 0%).



Conclusion: Liver fibrosis quantified by CPA analysis is an accurate predictor of clinical outcomes in patients with NAFLD and may further stratify risk in patients with cirrhosis.

THU026

Non-alcoholic fatty liver disease phenotype and prevalence across the menopause spectrum in women living with HIV

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Background and Aims: Both menopause and non-alcoholic fatty liver disease (NAFLD) are major metabolic events with potential systemic effects. The objective of the study was to describe natural history of NAFLD during menopause transition and the interplay between these two conditions in women living with HIV (WLWH).
Method: This was a cross-sectional study of consecutive WLWH attending Modena HIV Metabolic Clinic in 2018–2019. Women with hazardous alcohol intake and hepatitis B or hepatitis C virus co-infection were excluded. NAFLD and significant liver fibrosis were assessed with transient elastography and defined as controlled attenuation parameter (CAP) >248 dB/m and as liver stiffness measurement > = 7.1 kPa respectively. Menopause was determined according to STRAW criteria including 4 periods: reproductive, transitional, early and late menopause. Due to low absolute number of NAFLD cases, these criteria were further simplified dividing WLWH as “pre-menopause” if being in the first two periods and “post-

menopause" if being in the last two periods. Two logistic regression models were built to explore predictors associated with NAFLD in pre-menopause and post-menopause periods, using as covariates metabolic and anthropometric variables.

Results: We analyzed 296 WLWH with mean age = 54.3 (+−7.9) years, current median CD4 = 710 μL (IQR = 543–896) and HIV RNA undetectability in 98.3% of cases. Overall, NAFLD and significant fibrosis prevalence in WLWH were 33.8% and 11.8% respectively. NAFLD and significant fibrosis were observed in 33.3% and 7.4% in reproductive, 29.4% and 11.8% in menopause transition, 32.6% and 12.9% in early menopause and 56.3% and 12.5% in late menopause respectively (p = 0.07 and p = 0.66). Table shows characteristics between WLWH with NAFLD in reproductive and menopause period. In two multivariate logistic models, HIV duration, lipoatrophy, CD4/CD8 ratio and obesity were not associated with an increased risk of NAFLD in pre-menopause and post-menopause, while the HOMA was the only co-variate to predict NAFLD in post-menopausal WLWH (OR = 0.38, 0.15–0.8; p = 0.03).

Variable	Pre-menopause NAFLD	Post-menopause NAFLD	p
	32 (34.4%)	61 (65.6%)	
Age, years, mean (±SD)	49.5 (±6.6)	57.8 (±6.6)	
BMI, kg/m², mean (±SD)	26.9 (±5.9)	26.3 (±7.1)	0.56
Waist circumference, cm, mean (±SD)	94.1 (±13.6)	91.3 (±10.3)	0.44
Obesity (%)	8 (25%)	11 (18.3%)	0.63
HIV duration, years, median (IQR)	23.8 (14.8-27.6)	26.3 (23.9-30.3)	0.03
Nadir CD4, median, c/μL, median (IQR)	251 (145-385)	199 (100-277)	0.11
Current CD4, median, c/μL, (IQR)	727 (533-931)	716 (575-923)	0.75
CD4/CD8 ratio, mean (±SD)	1.1 (±0.5)	1.2 (±0.6)	0.67
Type 2 diabetes (%)	4 (12.5%)	16 (16.2%)	0.21
Multimorbidity (%)	5 (15.6%)	46 (75.4)	<0.001
FIB 4, mean (±SD)	1.2 (±0.9)	1.5 (±0.7)	0.09
LDL cholesterol, mg/dl, mean (±SD)	129 (±41.5)	125 (±41.2)	0.67
HDL cholesterol, mg/dl, mean (±SD)	62.6 (±16.3)	57.7 (±13.7)	0.21
Triglycerides, mg/dl, mean (±SD)	103.7 (±40.7)	143.1 (±77)	0.01
HOMA, mean	2.4 (±1.2)	3 (±1.9)	0.54

Conclusion: Prevalence and phenotype of NAFLD and liver fibrosis did not differ across the menopause in WLWH, suggesting that more complex immune-metabolic pathways, not captured by STRAW criteria, are involved in NAFLD natural history in aging WLWH.

THU028

The association with low skeletal muscle mass and carotid atherosclerosis in patients with non-alcoholic fatty liver disease

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Background and Aims: Although low skeletal muscle mass (LSMM) and carotid atherosclerosis are associated with non-alcoholic fatty liver disease (NAFLD), respectively, associated with LSMM and subclinical atherosclerosis in patients with NAFLD has not been established. We investigated whether LSMM was associated with carotid atherosclerosis in patients with NAFLD.

Method: From January 2010 to November 2019, a total 683 ultrasound-confirmed NAFLD patients who performed carotid ultrasound from health promotion center of Yeungnam University Hospital were included in the analysis. LSMM was defined as Appendicular skeletal muscle (ASM) using bioelectrical impedance analysis divided by body mass index (ASM/BMI). Using carotid ultrasound and Doppler, elevated carotid intima media thickness (IMT) (>1 cm) and presence of carotid plaque were measured, which are defined as indicators of early atherosclerosis.

Results: Of 683 patients with NAFLD, 75 (11.0%) were diagnosed with LSMM. The LSMM group were older (52.9 vs. 49.2 years, p = 0.011), had higher BMI (29.0 vs. 26.3 kg/m², p = 0.001), proportion in presence of insulin resistance (53.3 vs. 33.2%, p = 0.001), proportion of elevated IMT (33.3 vs. 14.5%, p = 0.001) compared to non-LSMM group. In patients with NAFLD, the presence of LSMM was associated with elevated IMT (odd ratios [OR] = 2.26 to 2.95, p < 0.05) and carotid plaque (OR = 2.05 to 2.90, p < 0.05) using adjusted models for age, sex, diabetes, hypertension obesity, waist circumference, hyperuricemia, lipid profile, aminotransferase, gamma-glutamyl transferase, homeostatic model assessment-insulin resistance, and high sensitivity C-reactive protein (Figure). In patients with obese NAFLD as a subgroup, the presence of LSMM was associated with elevated IMT (odd ratios [OR] = 2.44 to 3.30, p < 0.05) and carotid plaque (OR = 2.56 to 3.54, p < 0.05) using adjusted model.

Conclusion: LSMM may be associated with elevated IMT and presence of carotid plaque in patients with NAFLD, independently classic metabolic factors and insulin resistance.

THU029

Gender difference and hepatocellular carcinoma incidence in non-alcoholic steatohepatitis patients with advanced liver fibrosis

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Background and Aims: Hepatocellular carcinoma (HCC) is known to be more common in males than females. However, there are limited data regarding the effect of gender difference on the incidence of HCC in non-alcoholic steatohepatitis (NASH) patients. The study aimed to evaluate the effect of gender difference on the risk of developing HCC in NASH patients with advanced fibrosis.

Method: We conducted a single-center retrospective cohort study, including patients with biopsy-proven NASH with F3/F4 fibrosis and NASH or cryptogenic cirrhosis who were evaluated at our institution between 2007–2016. The date of diagnosis (biopsy date or clinical evidence of cirrhosis) and the date of last abdominal imaging, liver transplantation or HCC diagnosed were used to assess follow-up time. Kaplan-Meier analysis was used to estimate the cumulative incidence. The incidence rate was calculated and multivariate cox-regression analysis were used to evaluate the association of risk factors and HCC occurrence.

Results: 1,197 patients were included. There were 131 patients with F3 fibrosis and 1,066 patients with cirrhosis. Among NASH cirrhosis patients, 452 were male and 614 were female. Median follow-up was 3.84 years (IQR 2.16, 6.27). There were no differences in baseline age, race, body mass index or metabolic risk factors. However, male patients had fewer follow-up years (3.39 VS 4.13 years, p < 0.001) and more decompensated cirrhosis at presentation (48.4 VS 41.0%, p < 0.001). HCC developed in 102 patients. The incidence rates in all

	Elevated IMT		Carotid plaque	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
LSMM_BMI in NAFLD patients (yes vs. no)				
Unadjusted	2.95 (1.74-5.02)	<0.001	2.85 (1.51-5.39)	0.001
Age, sex adjusted	2.26 (1.26-4.04)	0.006	2.05 (1.03-4.08)	0.004
Model 1	2.28 (1.27-4.08)	0.005	2.20 (1.10-4.40)	0.026
Model 2	2.28 (1.27-4.08)	0.005	2.90 (1.40-6.04)	0.004
Model 3	2.26 (1.26-4.04)	0.006	2.74 (1.30-5.78)	0.008

LSMM, low skeletal muscle mass; OR, odds ratio; BW, body weight; BMI, body mass index; CI, confidence interval; NAFLD, non-alcoholic fatty liver disease; ASM: appendicular skeletal muscle mass.

Model 1: Age, sex, presence of diabetes, and hypertension

Model 2: Further adjusted for presence of obesity, waist circumference, and hyperuricemia

Model 3: Further adjusted for total cholesterol, triglyceride, and high-density lipoprotein, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, homeostatic model assessment-insulin resistance, and high sensitivity C-reactive protein

Figure: (abstract: THU028)

cirrhotic patients (both male and female), male with cirrhosis and female with cirrhosis were 2.07/100 person-year, 3.51/100 person-year and 1.19/100 person-year, respectively. Multivariable analysis showed that male gender (IRR 3.60; 95%CI 2.35–5.50, p < 0.001), clinical decompensation at presentation (IRR 1.63; 95%CI 1.08–2.46, p = 0.021) and older age (IRR 1.04; 95% CI 1.02–1.06, p < 0.001) were independent variables associated with HCC development. Among patients with F3 fibrosis, no HCC development was observed during the total of 674 follow-up years.

Conclusion: Gender has a significant impact on HCC development among patients with NASH-related cirrhosis. Further longitudinal studies are needed to better elucidate the reasons for these differences.

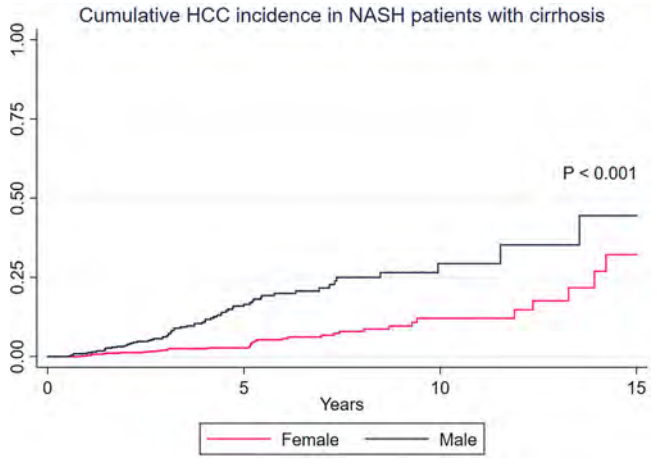

Figure: (abstract: THU029)

THU030

Advanced liver fibrosis predicts poor cardiovascular outcomes in patients with type 2 diabetes

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Background and Aims: Atherosclerotic cardiovascular disease (ASCVD) is the principal cause of death in patients with type 2 diabetes (T2D). T2D is closely associated with non-alcoholic fatty liver disease (NAFLD); liver fibrosis is poorly prognostic in NAFLD patients. Thus, we explored whether liver fibrosis predicted the risk of ASCVD in patients with T2D.

Method: A total of 1,604 patients who had commenced oral anti-diabetic drugs to treat newly diagnosed T2D between 2006 and 2010 were recruited. NAFLD was defined as a hepatic steatosis index (HSI) >36. Liver fibrosis was assessed using the fibrosis-4 index (FIB-4) and the NAFLD fibrosis score (NFS). Advanced liver fibrosis was defined as an FIB-4 score >3.25 and an NFS >0.676. The predicted ASCVD risk was calculated using the 10-year ASCVD risk prediction model of the 2013 ACC/AHA (American College of Cardiology / American Heart Association) guideline.

Results: NAFLD and advanced liver fibrosis were identified in 920 (57.4%) and 39 (2.4%) patients respectively. During the follow-up period (median 80.1 [interquartile range 40.2–115.2] months), ASCVD developed in 199 (12.4%) patients. The predicted and observed ASCVD risks were significantly higher in patients with than without advanced liver fibrosis (28.0 vs. 18.1%, p = 0.001 and 23.1 vs. 12.1%, p = 0.041). Advanced liver fibrosis, as revealed by the NFS, independently predicted an increased risk of ASCVD (hazard ratio = 1.232, 95% confidence interval 1.071–1.418, p = 0.004) as did older age and hypertension. The cumulative incidence of ASCVD was significantly higher in patients with than without advanced liver fibrosis (p = 0.031, log-rank test). Among patients with NAFLD, the cumulative

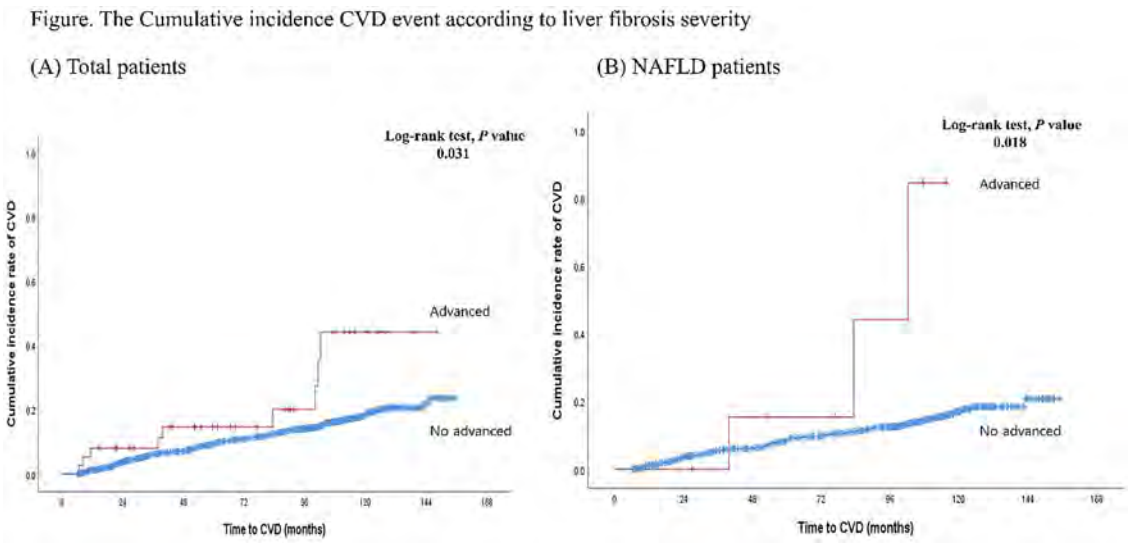

Figure: (abstract: THU030)

incidence of ASCVD was also significantly higher in patients with than without advanced liver fibrosis (p = 0.018, log-rank test).
Conclusion: Advanced liver fibrosis independently predicted an increased risk of ASCVD in patients who had commenced anti-diabetic drugs to treat newly diagnosed T2D. Thus, assessment of liver fibrosis might allow physicians to optimize the timing of appropriate preventative or diagnostic cardiovascular interventions in such patients.

THU031

Histological renal damage and eligibility for kidney donation are worse in patients with biopsy-proven non-alcoholic steatohepatitis compared with simple steatosis

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) has been related with multi-organ comorbidities. Nevertheless, the relationship with kidney disease has been poorly investigated.
The aim of this study was to verify whether patients with NAFLD have higher risk of kidney disease evaluated during the process of eligibility for kidney donation and histological scores of damage.
Method: This study is based on the register of Reference Center for Organ Transplantation of Emilia-Romagna, which contains data collected during the work-up for the determination of eligibility of potential donors.
After having excluded patients with incomplete work-up (771), with non-NAFLD liver diseases (153) and whose liver was utilized for transplantation without a preliminary biopsy (414), 722 consecutive subjects ≥ 18 y submitted to liver biopsy from 2008 to 2018 were enrolled (mean age 62y, range 18–89). Patients were divided in three groups based on the review of histological reports: healthy liver (n = 166: no steatosis, fibrosis or inflammation), simple steatosis (n = 358: micro or macrovescicular steatosis involving >5% of the parenchyma, no fibrosis and inflammation), and non-alcoholic steatohepatitis (NASH, n = 198: fibrosis or inflammation). The risk of having kidneys not eligible for donation was assessed in these groups.
Finally, 403 of these 722 had been submitted to both liver and kidney biopsy (62y, range 18–89). The risk of kidney damage (assessed with Karpinski score) was verified in this population.
Results: Distributions of age, diabetes and hypertension were similar in the study groups.
NASH showed higher risk of having kidneys not eligible for donation than healthy liver. Odds ratios (OR) were: left kidney 1.9, p = 0.005; right kidney 1.7, p = 0.017. No increased risk was found in simple steatosis (p = 0.259 and p = 0.258).
A higher risk of histological kidney damage (Karpinski score ≥ 3, Figure 1) was found in NASH group (OR: left kidney 2, p = 0.022; right kidney 2.6, p = 0.002) but not in simple steatosis (p = 0.763 and 0.200).
Risk of vascular damage involving >20% of the glomeruli (Karpinski vascular score ≥ 2) was found in NASH (right kidney OR 1.9, p = 0.029) but not in simple steatosis (p = 0.405).
Conclusion: This study shows that NASH is associated with an increased risk of biopsy-proven kidney damage, not present in simple steatosis. These findings might indirectly suggest the presence of generalized inflammatory and fibrotic pathways in the subset of patients developing NASH.

THU032

Evolution of hepatic fibrosis and steatosis during long-term use of metformin in patients with type 2 diabetes

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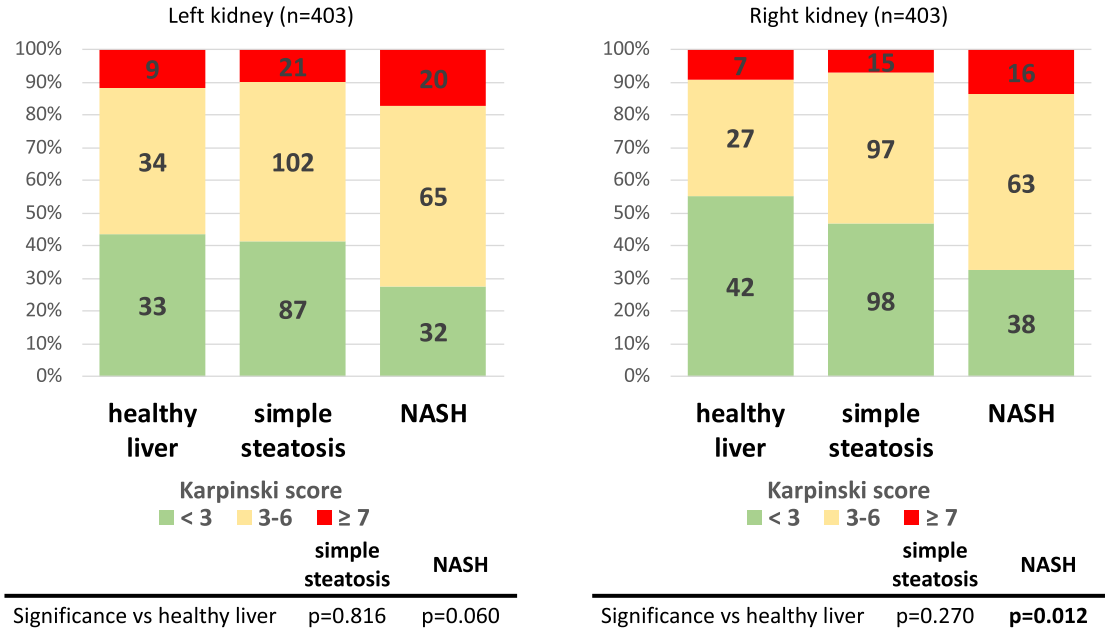
Background and Aims: The main therapeutic aim in patients with type 2 diabetes (T2D) is control of the serum glucose level. Metformin is widely used as a first-line antidiabetic agent. The prevalence of chronic liver diseases, such as non-alcoholic fatty liver disease, is high in patients with T2D. However, few studies have investigated the evolution of liver fibrosis and steatosis during long-term use of metformin in patients with T2D.
Method: From 2006 and August 2010, patients newly diagnosed T2D who received metformin were recruited. Patients were excluded if they had chronic liver diseases other than non-alcoholic fatty liver diseases, an insufficient follow-up period (<2 years), or insufficient laboratory information for calculation of noninvasive liver fibrosis and steatosis indices (i.e., fibrosis-4 index [FIB-4] and hepatic steatosis index [HSI]) at enrollment and at 2 years. Significant liver



	simple steatosis	NASH
Significance vs healthy liver	p=0.816	p=0.060

	simple steatosis	NASH
Significance vs healthy liver	p=0.270	**p=0.012**

Figure 1. Distribution of Karpinski classes (Karpinski score <3, 3-6 and ≥7) in patients with healthy liver, simple steatosis and NASH.

Figure: (abstract: THU031)

fibrosis was defined as FIB-4 score of >2.67 and fatty liver was defined as HSI score>36.0.

Results: In total, 1,292 patients were finally enrolled. The mean age of the study population (732 men and 560 women) was 60.8 years. The mean body mass index and mean serum glucose, hemoglobin A1c, and aspartate and alanine aminotransferase levels were 25.1 kg/m^2, 143 mg/mL, 7.3%, 26.5 IU/L, and 30.1 IU/L, respectively. The mean FIB-4 and HSI scores were 1.38 and 27.3, respectively. At enrollment, 83 (6.4%) patients had significant liver fibrosis, while 429 (33.2%) patients had fatty liver. After 2 years of metformin treatment, the mean FIB-4 score was significantly increased (1.38 to 1.51, $p < 0.001$), whereas the mean HSI was decreased (27.3 to 26.5, $p < 0.001$). In addition, significant liver fibrosis was developed in 52 (4.0%) patients, whereas the proportion of patients with fatty liver was stable or reduced (33.2% to 27.9% [n = 335], $p < 0.001$). The HbA1c levels were not significantly different between patients with and without significant liver fibrosis at baseline (7.3% vs. 7.4%, $p = 0.368$) and 2 years (7.0% vs. 6.8%, $p = 0.101$). Only age (odds ratio [OR] = 1.094, 95% CI, 1.038–1.153, $p = 0.001$) was independently associated with the risk of developing significant liver fibrosis after 2 years of metformin treatment. In the subgroup of 712 (55.1%) patients who were followed up for 5 years, the FIB-4 score tended to increase (mean 1.80 at 5 years), whereas the HSI score remained stable (mean 26.4 at 5 years). During the study period (median 97.1 months), 2 (0.3%) and 118 (19.1%) patients developed hepatocellular carcinoma and cardiovascular events, respectively.

Conclusion: During long-term metformin treatment, female patients with T2D had a significantly threefold higher risk of liver fibrosis progression. Therefore, early recognition of liver fibrosis progression and the use of appropriate medical interventions should be considered for female patients with T2DM.

THU033

Incidence and risk factors for cardiovascular events in patients with advanced fibrosis due to non-alcoholic steatohepatitis: data from the phase 3 STELLAR trials

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Background and Aims: Nonalcoholic steatohepatitis (NASH) is associated with an increased risk of cardiovascular (CV) disease, but the impact of advanced fibrosis is unclear. Our objective was to describe the incidence and risk factors for major adverse CV events (MACE) in patients with NASH and advanced fibrosis enrolled in two phase 3 trials.

Method: Patients with advanced fibrosis (F3-F4) due to NASH (NAS ≥ 3) were enrolled in two placebo-controlled trials of selonsertib (STELLAR). The trials were discontinued after 48 weeks due to lack of

efficacy; hence treatment groups were combined. The incidence of adjudicated MACE was assessed via Poisson regression and associations between baseline demographic and clinical parameters (eg. fibrosis stage, NAS, ELF, ALT, history of CV disease, diabetes mellitus [DM], smoking, hypertension, lipids, hsCRP, and use of statins or GLP-1 receptor agonists) were determined via Cox regression.

Results: 1679 patients with bridging fibrosis (n = 802) or cirrhosis (n = 877) were included (median age 59 yrs, 60% female, 74% DM, 68% BMI ≥ 30 kg/m^2). During a median follow-up of 15.8 months (IQR 13.8, 18.2), 16 patients (1.0%; n = 2 with F3 [0.2%], n = 14 with F4 [1.6%]) had a total of 18 MACE (stroke [n = 5], coronary revascularization [n = 6], myocardial infarction [n = 4], and hospitalization for cardiac failure [n = 2] or unstable angina [n = 1]). The overall incidence (95% CI) of a first MACE was 0.72 per 100 person-years (pyrs) of follow-up (0.41, 1.17); the incidence was significantly higher in patients with cirrhosis (1.22 per 100 pyrs [0.67, 2.05] than those with F3 fibrosis (0.19 per 100 pyrs [0.02, 0.67]; hazard ratio [HR] 6.45 [95% CI 1.46, 28.36]; p = 0.0137). Additional risk factors for MACE in univariate analysis included older age (≥ vs <65 years: HR 2.87 [95% CI 1.08, 7.64]), baseline ELF score (HR per 0.5 units: 1.30 [1.03, 1.63]), and prior history of CV disease (HR 3.17 [1.10, 9.13]), but not sex, DM, smoking, hypertension, obesity, use of statins or GLP-1 receptor agonists, or baseline ALT, NAS, platelets, INR, FIB-4, total or LDL cholesterol, triglycerides, or hsCRP.

Conclusion: In this clinical trial population of patients with advanced fibrosis due to NASH, the incidence of adjudicated MACE was ~7 per 1,000 person-years. Patients with greater fibrosis burden at baseline – measured by biopsy or ELF – those ≥ 65 years of age, and patients with a prior history of CV disease, are at the greatest risk of adverse CV outcomes.

THU034

A substantial number of patients with non-alcoholic fatty liver disease and type 2 diabetes have advanced liver fibrosis with a normal serum alanine transaminase

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Background and Aims: Type 2 diabetes mellitus (T2DM) is the strongest risk factor for developing non-alcoholic fatty liver disease (NAFLD). NICE does not recommend screening for NAFLD in T2DM. NICE does recommend assessment of fibrosis in NAFLD. Over half of patients with NAFLD and a normal alanine transaminase (ALT) have non-alcoholic steatohepatitis, which is associated with fibrosis, cirrhosis and hepatocellular carcinoma. Our aim was: (1) establish the association between T2DM and advanced fibrosis in the liver clinic; (2) describe the proportion of individuals with advanced fibrosis and normal ALT.

Method: We generated a dataset of patients with NAFLD who had a FibroScan® in the liver clinic in 2018. We used a cross-sectional study design to analyse baseline characteristics of all patients including sex, age, body mass index (BMI), presence of T2DM, ALT and LSM.

Results: 277 patients attended the clinic with a diagnosis of NAFLD. Mean age (±SD) was 56.6 years (±12.9). 156/277 (56.3%) patients were male. 111/277 (40%) patients had T2DM. 69/111 (62%) patients with T2DM had advanced fibrosis (LSM ≥ 8.7 kPa). 41/166 (25%) patients without diabetes had advanced fibrosis. T2DM was positively associated with advanced fibrosis, crude odds ratio (OR) 5.01 [95% CI 2.97–8.43]. We performed multinomial logistic regression with age and sex as covariants. T2DM remained positively associated with advanced fibrosis after adjustment for age and sex (adjusted OR 5.02 [95% CI 2.96–8.54]). 30/111 (27.0%) patients with T2DM had a normal ALT (reference range 10–40 U/L) with advanced fibrosis.

Table: Baseline characteristics in patients with NAFLD grouped by presence/absence of T2DM

	All patients n = 277	
	T2DM	No T2DM
Total number	111	166
Male sex (%)	56 (50)	100 (60.0)
Age (years)	59.2 (57.2–61.3)	54.5 (52.3–56.7)
BMI (kg/m^2)	33.5 (32.3–34.6)	31.8 (30.9–32.6)
LSM (kPa)	13.5 (10.4–16.6)	9.0 (6.2–11.8)
Patients with advanced fibrosis ≥ 8.7 kPa (%)	69 (62.0)	41 (25.0)
Patients with normal ALT (%)	52 (46.8)	71 (42.8)
Normal ALT and advanced fibrosis (≥ 8.7 kPa) (%)	30 (27.0)	16 (9.6)

Conclusion: Advanced liver fibrosis occurred more than twice as frequently in patients with T2DM than those without T2DM. There was a strong association between T2DM and advanced fibrosis. A considerable proportion of patients with T2DM had advanced fibrosis and normal ALT. This result has significant implications for health care professionals managing patients with T2DM who may not test for liver disease when ALT levels are normal.

THU035

Unlike HbA1c level and the amount of visceral adipose tissue, the presence and severity of NAFLD do not predict the occurrence of major adverse cardiovascular events in an obese Belgian population

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Background and Aims: Cardiovascular disease is the most important cause of morbidity and mortality in non-alcoholic fatty liver disease (NAFLD) patients. This study aimed at determining the predictive value of NAFLD grade at baseline, as well as other clinical parameters, with respect to the occurrence of major adverse cardiovascular events (MACE) during follow-up.

Method: Patients who consulted the metabolic unit of the Antwerp University Hospital between 2006–2012 and underwent a liver biopsy because of a clinical suspicion of NAFLD, were included consecutively with informed consent. The FLIP algorithm was used to define NAFLD grade: no NAFLD, non-alcoholic fatty liver (NAFL), non-fibrotic non-alcoholic steatohepatitis (NASH, <F2) and fibrotic NASH (≥ F2). MACE were defined as the occurrence of stroke, (non) ST elevation myocardial infarction [(N)STEMI)] or unstable angina. The occurrence of MACE was examined by reviewing the in-hospital and

the nation-wide accessible electronic patient files. Statistical analysis was performed by Cox regression.
Results: 323 patients (M:F 99:224) were included with a mean age of 44 ± 12 y and a mean BMI of 39.5 ± 6.4 kg/m^2. Liver biopsy showed no NAFLD in 69, NAFL in 93, non-fibrotic NASH in 126 and fibrotic NASH in 35 patients. Glucose tolerance testing was normal in 187, impaired in 109 and showed a new diagnosis of type 2 diabetes in 27 patients. Mean blood pressure was 128 ± 14/76 ± 9 mmHg and 31% of patients were treated for hypertension. Cholesterol, HDL and triglyceride levels were 204 ± 41, 49 ± 14 and 153 ± 80 mg/dL resp. and 10% of patients were on a statin, while 47% had an active smoking habit.
Over a mean follow-up period of 4.6 ± 3.6 y, MACE were registered in 10 patients (2 no NAFLD, 2 NAFL, 4 non-fibrotic NASH and 2 fibrotic NASH). NAFLD grade did not show predictive value with respect to the occurrence of MACE (p = 0.799). In contrast, baseline HbA1c level and the amount of visceral adipose tissue, as assessed by computed tomography, were found to be strong predictors [resp. HR 4.741 per % (95% CI 1.515–14.651), p = 0.007 and HR 1.010 per cm^2 (95% CI 1.003–1.017), p = 0.003]. Conversely, no predictive value was shown for cholesterol, HDL or triglyceride levels, nor for sex or smoking habit. Concerning the systolic blood pressure, although no significant predictive value was demonstrated with respect to MACE, significance was reached with respect to the subgroup of acute coronary syndrome patients (n = 7), comprising unstable angina and (N)STEMI [HR 1.058 per mmHg (95% CI 1.015–1.103), p = 0.008].
Conclusion: In this population of obese patients, NAFLD grade wasn't shown to be a significant predictor of the occurrence of MACE during a mean follow-up period of 4.6 y. Conversely, HbA1c level and the amount of visceral adipose tissue were strong predictors, underlining the importance of insulin resistance and central obesity in the development of cardiovascular disease.

THU036

Association of FIB-4 score with disease progression in real-world populations diagnosed with NAFLD/NASH or at risk of NASH in US clinical practice

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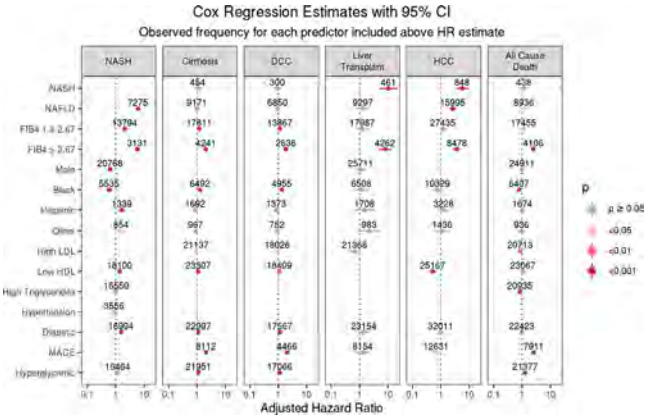
Background and Aims: Patients with NAFLD are at increased risk of developing advanced liver disease. Using data from clinical practices in the US, we assessed the risk of NASH, cirrhosis, decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), and liver transplant (LTX) in populations with diagnosed NAFLD or NASH or at risk of NASH based upon clinical criteria.
Method: Data obtained from a proprietary EMR database were limited to adult patients with diagnosed NAFLD without NASH (ICD10 K76 and ICD9 equivalent without evidence of NASH) or NASH (ICD10 K75.81) and without viral hepatitis or alcohol abuse. Index date was the first calculable FIB4 between Jul 2015 to Jun 2017 with >1 y history and >2 y follow-up or to death. Cox proportional models were used to determine hazard ratios (HR) between groups, stratified by age and BMI group status at index. All multiple regression models used complete-case analysis and included diagnosis group, FIB4, race/ethnicity, and all covariates with p < 0.200 by individual models.
Results: Of 30 million adult patients, 81108 met all study criteria with 22% (17582) NAFLD without NASH, 1% (914) NASH, and 77% (62612) RISK (without NAFLD or NASH diagnosis) at index. Mean follow up was 34.8 months (32.3 NASH, 32.4 NAFLD without NASH, 34.9 RISK). Significant differences were observed between 2+ diagnosis groups for age, gender, race, BMI, comorbidities, and laboratory measures HDL and LDL cholesterol, triglycerides, blood glucose, platelets, and FIB4 at index. The proportion of patients with FIB4 ≥ 2.67 was significantly higher for NASH (31%, 283) compared to NAFLD without NASH (12%, 2107, p < 0.001) which was significantly higher than RISK (11%, 6820, p < 0.001). Results from Cox regression models indicated FIB4 ≥ 2.67 had the highest or 2nd highest HR for all evaluated outcomes [Figure]. Other variables associated with high HR were: index NAFLD without NASH for NASH outcome, major cardiovascular events (MACE) for cirrhosis and DCC outcomes, index NASH for LTX outcome, index NASH and index NAFLD without NASH for HCC outcome, and MACE for all-cause death. HR for cirrhosis and DCC outcomes were not significantly different between NASH, NAFLD without NASH, and RISK covariates.



Conclusion: In this real-world study of patients with diagnosed NAFLD/NASH or at risk of NASH, FIB4 ≥ 2.67 was singularly associated with the development of advanced liver disease by all outcomes evaluated.

THU037

Association of FIB-4 score with major cardiovascular events (MACE) in real-world populations diagnosed with NASH or NAFLD in US clinical practice

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Background and Aims: Patients with NAFLD have higher incidence of cardiovascular disease (CVD) which is considered the most common cause of mortality in these patients. Using data from US clinical practices, we assessed incidence of MACE as indicated by coronary artery bypass grafting, coronary revascularization, heart failure (HF), myocardial infarction (MI), stroke, and unstable angina in populations with diagnosed NAFLD or NASH.
Method: Data obtained from a proprietary EMR database were limited to adult patients with diagnosed NAFLD without NASH (ICD10 K76 and ICD9 equivalent without evidence of NASH) or NASH (ICD10 K75.81) and without viral hepatitis or alcohol abuse. Index date was the first calculable FIB4 between Jul 2015 to Jun 2017 with >1 y history and >2 y follow-up or to death. MACE assignments were based upon ICD, CPT, and HCPCS codes. Cox proportional models were used to determine hazard ratios (HR) between groups, stratified by age at index. All multiple regression models used complete-case analysis and included diagnosis group, FIB4, race/ethnicity, obesity, and all covariates with p < 0.200 by individual models.

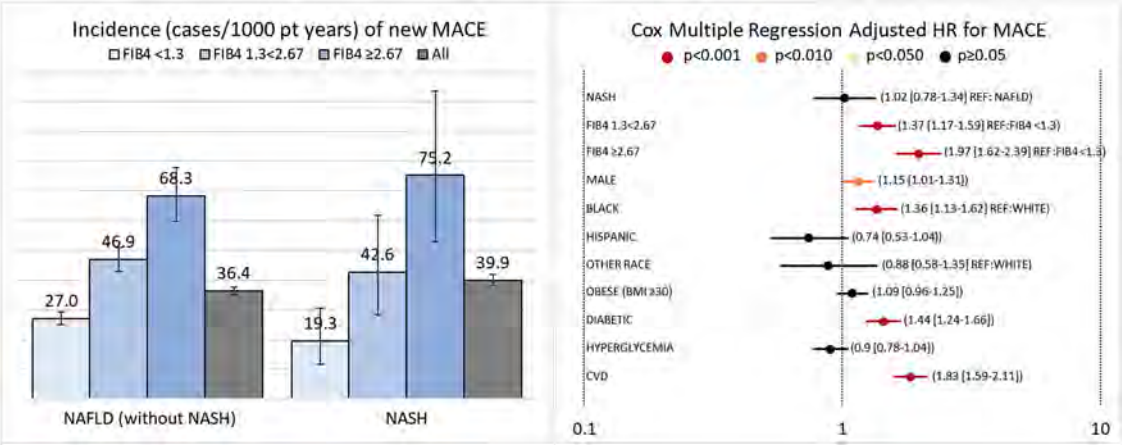

Figure: MACE incidence rates and 95% CI (left) and Cox multiple regression adjusted hazard ratios (right).

Results: Of 30 million patients, 18496 met all study criteria with 95% (17582) NAFLD without NASH and 5% (914) NASH at index. Mean follow up was 32.4 months. MACE prior to index was significantly higher for NAFLD without NASH (15%, 2620) vs NASH (13%, 118, $p < 0.001$). The most common MACE prior to index were HF (10%, 1785 NAFLD without NASH; 10%, 88 NASH) and MI (7%, 1258, NAFLD without NASH; 5%, 49 NASH). In 15758 patients without MACE prior to index, incidence rates (cases/1000 person-years) of any MACE were not significantly different between NAFLD without NASH (36.4) and NASH (39.9, $p = 0.430$). Within each diagnosis group, MACE incidence increased with increasing fibrosis. [Figure Left] Results from Cox multiple regression analysis indicated FIB4 ≥ 2.67 had the highest HR for MACE incidence followed by history of CVD, type II diabetes, and black. [Figure Right].
Conclusion: In this real-world study of patients with diagnosed NAFLD or NASH, the incidence of MACE increased with increasing fibrosis and FIB4 ≥ 2.67 was associated with the highest HR by Cox multiple regression.

THU038

Relevance of social support and severity of liver disease in biopsychosocial profiles of patients with non-alcoholic fatty liver disease

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Background and Aims: It is unknown how social support and the progression of liver damage influence the biopsychosocial profile of patients with non-alcoholic fatty liver disease (NAFLD). Therefore, the objectives of this study were to: 1) Analyse whether there are differences between patients with absence and presence of non-alcoholic steatohepatitis (NASH) in quality of life, mental health and coping strategies, based on high or low perceived social support, 2) Analyse the influence of liver severity levels on these variables: NAFLD and NASH patients, with and without significant fibrosis (SF), considering the data on the general Spanish population for quality of life.
Method: Four hundred and ninety-two biopsy-proven NAFLD patients (290 men and 202 women, mean age 54.90 ± 11.74) were evaluated using the *SF-12, CLDQ-NAFLD, HADS, BDI-II, COPE-28* and *MSPSS* instruments. To respond to the first objective, four groups (G_1, n = 201, absence of NASH; G_2, n = 291, presence of NASH; G_3, n = 245, high social support; G_4, n = 247, low social support) were formed and a 2 × 2 factorial ANOVA was performed. To respond to the second objective, four groups were set up by severity, classified according to the steatosis, activity and fibrosis score (SAF score; G_a, n = 70, NAFLD without SF; G_b, n = 66, NASH with SF; G_c, n = 87, NAFLD with SF; G_d, n = 33, NASH without SF), which were compared using the Snedecor *F* test (post hoc comparisons: Tukey) and Welch *U* test (post hoc comparisons: Games-Howell), depending on whether homoscedasticity was met or not. The *t* test for independent samples was also applied to compare the quality of life (*SF-12*) with the general Spanish population. Cohen's *d* (for continuous variables) and *w* (for categorical variables) were used as indices of effect size.
Results: Interactive effects were found in vitality ($p = 0.047$), activity ($p = 0.005$), anxiety ($p = 0.044$) and denial ($p = 0.042$). Specifically, NASH patients (G_2) showed a higher-risk biopsychosocial profile when they perceived less social support. Furthermore, regardless of NASH, patients with low social support (G_4) had a lower quality of life, worse mental health and more maladaptive coping than those with high social support (G_3). NAFLD (G_c) and NASH (G_b) patients with SF showed lower quality of life than NAFLD (G_a) and NASH (G_d) patients without SF, or the general Spanish population. Patients with SF (G_b) also had worse mental health and coping than those without SF (G_a and G_d).
Conclusion: Regardless of the presence or absence of NASH, low perceived social support and SF were associated with a higher-risk biopsychosocial profile in NAFLD: worse quality of life and mental health, and more maladaptive coping. These findings suggest the relevance of integrating the psychological evaluation and intervention in protocols for following up on these patients.

THU040

NAFLD is a rising cause of HCC in women in a prospective populational cohort spanning 24 years (1990–2014)

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Background and Aims: There is conflicting data regarding the epidemiology and natural history of hepatocellular carcinoma (HCC) arising on the background of non-alcoholic fatty liver disease

(NAFLD-HCC). We aimed to assess the natural history and epidemiology of all patients with NAFLD-HCC between 1990 and 2014 in a well-defined population.

Method: All HCC cases resident in the canton of Geneva, Switzerland, diagnosed between 1990–2014 were identified from the prospective Geneva cancer registry and all data was manually checked and completed using Geneva university hospital electronic health records. NAFLD-HCC was diagnosed when specifically stated or when other causes of liver disease were excluded in the presence of type 2 diabetes, metabolic syndrome or obesity.

Results: 920 patients were diagnosed with HCC in the canton of Geneva between 1990–2014. Major aetiologies of underlying liver disease were alcohol (43.2%), hepatitis C and B viruses (20.7% and 9.1% respectively), and NAFLD (8.3%). The 76 NAFLD-HCC subjects were significantly older, had higher rates of obesity (46.6% vs 13.4%, $p < 0.001$), diabetes (73.0% vs 39.6%, $p < 0.001$) and were more commonly female (31.6% vs 18.6%, $p = 0.006$). The age-standardized incidence (ASI) of HCC increased between 1990–94 to 2010–14 from 11.6 to 12.8/100,000 in men and 1.8 to 3.3/100,000 in women. The proportion of NAFLD-HCC increased significantly in both sexes, but in particular in women from 0% in 1990–94 to 30% in 2010–14 (Figure).

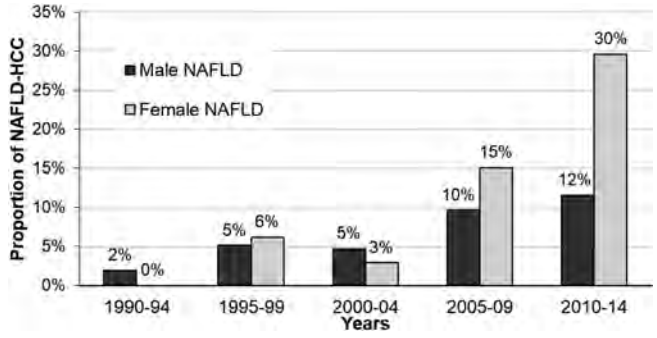

Figure: Proportion of NAFLD-HCC by sex between 1990–2014.

Conclusion: In a prospective populational cohort of HCC subjects spanning 24 years, NAFLD-HCC accounted for 8% of all HCCs. Compared to non-NAFLD-HCC, NAFLD-HCC patients were older, more comorbid and more frequently female. NAFLD is a rising cause of HCC, in particular in women. This study underlines the specific clinical characteristics of NAFLD-HCC, which will help to guide future recommendations and research.

THU041

Muscle fat infiltration in obese patients is associated with NAFLD related fibrosis severity - results from a prospective imaging study

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Background and Aims: The association between NAFLD and visceral adipose tissue or sarcopenia has been reported, although results are discordant. The goal of this study is to analyze the spectrum of NAFLD among obese patients recruited prospectively and to detect clinical, biological and imaging data associated with steatosis or fibrosis.

Method: Baseline data of obese patients (BMI ≥ 30) randomized in a single center (Food4Gut study) were recorded. Transient elastography (TE) was done to quantify both liver steatosis by controlled attenuation parameter (CAP) measurement and liver fibrosis by liver stiffness measurement (LSM). Body composition was evaluated using bioelectrical impedance analysis. Subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), muscle areas and muscle fat infiltration (MFI) were measured on CT-scan images at the third lumbar level.

Results: Fifty-two Caucasian patients (mean age: 50 years, 50% male, mean BMI 35.8) were included. TE was successful in 49 patients (94%). XL probe was used in 20 patients (38%). Mean LSM was low (6.5 kPa). Mean CAP result was high (324 dB/m) with the majority of the patients (73%) presenting severe steatosis (CAP ≥ 296 dB/m). 12 patients (24%) had advanced fibrosis defined by LSM ≥ 7.8 kPa (M probe) or ≥ 6.4 kPa (XL probe). Factors associated with severe steatosis and advanced fibrosis are summarized in the table. Interestingly, severe steatosis was associated with higher muscle quantity and severe fibrosis with a lower muscle density index, compatible with MFI. In a multivariate logistic regression analysis, MFI index was the strongest predictor of advanced liver fibrosis.

Conclusion: In summary, among obese patients, a high proportion of severe steatosis was diagnosed and advanced liver fibrosis was suspected in 24% of the patients. MFI provides a robust, skeletal muscle-specific characteristic linked to advanced fibrosis in NAFLD,

Table: (abstract: THU041)

	Parameter	Light-moderate steatosis	Severe steatosis	p-value	No fibrosis	Advanced fibrosis	p-value
Clinical parameters	Age (years)	49.2	50.1	NS	49.8	50.0	NS
	Weight (kg)	97.5	108.1	0.035	101.0	119.2	0.0035
	BMI (kg/m²)	34.3	36.5	NS	34.8	39.2	0.059
	Waist (cm)	112.0	116.9	NS	112.7	124.6	0.027
Biological results	ALAT (UI/L)	28.1	45.3	0.0059	35.4	57.2	NS
	γGT (UI/L)	40.0	50.6	NS	45.4	55.8	NS
	Fasting glycemia (mg/dL)	95.1	109.2	0.013	106.4	103.1	NS
Bioimpedance analysis	R	479.9	438.9	NS	460.7	417.1	0.048
	Fat free mass (kg)	61.7	68.6	NS	63.9	76.3	0.0034
	Total body fat (kg)	37.8	39.4	NS	38.0	42.9	NS
CT scan data	Subcutaneous fat area (cm²)	340.4	363.1	NS	338.8	413.6	NS
	Visceral fat area (cm²)	197.3	275.4	0.0066	236.6	310.2	0.054
	Whole muscle area (cm²)	153.2	182.7	0.038	166.4	200.1	0.0086
	Skeletal muscle index (cm²/m²)	52.9	61.9	0.028	57.6	65.1	0.054
	Whole muscle density index (UH/cm²)	0.208	0.185	NS	0.200	0.163	0.0051

suggesting a muscle-liver axis in the pathogenesis of NAFLD complications.

THU042

Exercise performance in patients with non-alcoholic steatohepatitis

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Background and Aims: Prior studies indicate that those with nonalcoholic fatty liver disease (NAFLD) have poorer exercise capacity compared to age-matched controls. Moreover, cross-sectional data in those with NAFLD suggest an inverse correlation between disease severity and self-reported exercise intensity. The underlying contributors of poor exercise capacity in patients with NAFLD is unclear. Our aim was to evaluate exercise performance in patients with biopsy-proven nonalcoholic steatohepatitis (NASH).
Method: Patients with biopsy-proven NASH (n = 10), graded and staged according to the NASH Clinical Research Network grading and staging system, and controls (n = 11), those without a diagnosis of biopsy-proven NAFLD were recruited. Participants performed 10-intervals of vigorous-intensity interval training (30 seconds exercise, 60 seconds rest) on a Concept2 indoor rowing machine at 80–90% of predicted maximum heart rate (220-Age). Intensity was recorded after each interval using the BORG scale of perceived exertion. Age, BMI, distance, power output, and $BORG_{peak}$ were compared between groups using Exact-Wilcoxon rank sum test or Fisher's exact test. Generalized linear modeling was used to adjust for age, gender, and BMI.
Results: Mean ages of participants were 51.0 ± 14.9 in the NASH group and 42.4 ± 13.6 in controls, $p > 0.05$. BMI was higher in the NASH group (32.5 ± 3.3) compared to controls (26.6 ± 4.6). Mean power output (watts) over the 10 exercise intervals was significantly lower in the NASH group (103.6 ± 30.4) compared to controls (231.0 ± 140.4), $p < 0.01$. Total distance rowed (meters) after 10-intervals was also lower in the NASH group (987.2 ± 115.7) compared to controls (1266.6 ± 259.4), $p < 0.01$. $BORG_{peak}$ was lower in the NASH group (14 ± 1) compared to controls (17 ± 2), $p < 0.01$. After adjusting for age, gender, and BMI the difference in mean power output, total distance, and $BORG_{peak}$ all remained significant, $p < 0.01$.
Conclusion: Compared to controls, those with NASH have lower exercise power output, rowing distance, and perceived exercise intensity. Failure to reach perceived exercise intensity beyond steady state (BORG ≥ 17) may serve as a potential biomarker for poor metabolic function as well as an underlying contributor of poor exercise performance in those with NASH.

THU044

Obesity and alcohol intake modify the impact of genetic variants on the risk for incident liver disease in the general population

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Background and Aims: Genetic variants and modifiable lifestyle factors including abdominal obesity and alcohol intake are risk factors for liver disease. We studied the interaction between genetic variants, abdominal obesity and alcohol intake for incident advanced liver disease (ILD).
Method: Our study included 32,942 persons (mean age 50 yrs, 47% men) who participated in health-examination surveys (FINRISK1992–2012 or Health 2000) with available data on alcohol intake (median 26.0 g/wk), waist-hip ratio (WHR, mean 0.89) and genotypes associated with liver disease in PNPLA3, TM6SF2, MBOAT7, SERPINA1 and HFE. A genetic risk score (GRS) was calculated as the sum of these risk alleles. Data were linked with national health registers for liver-related outcomes (hospitalizations, malignancies, and death). Exclusions were baseline clinical liver disease or viral hepatitis. Analyses were adjusted for age, WHR and alcohol intake.
Results: TM6SF2 rs58542926 ($p < 0.05$) and SERPINA1 rs28929474 ($p < 0.02$) genotypes interacted significantly with WHR. Among carriers of these risk variants, the cumulative incidence of liver disease was significantly higher than non-carriers when WHR exceeded ~1.0, but not below WHR 1.0. The GRS showed a dose-

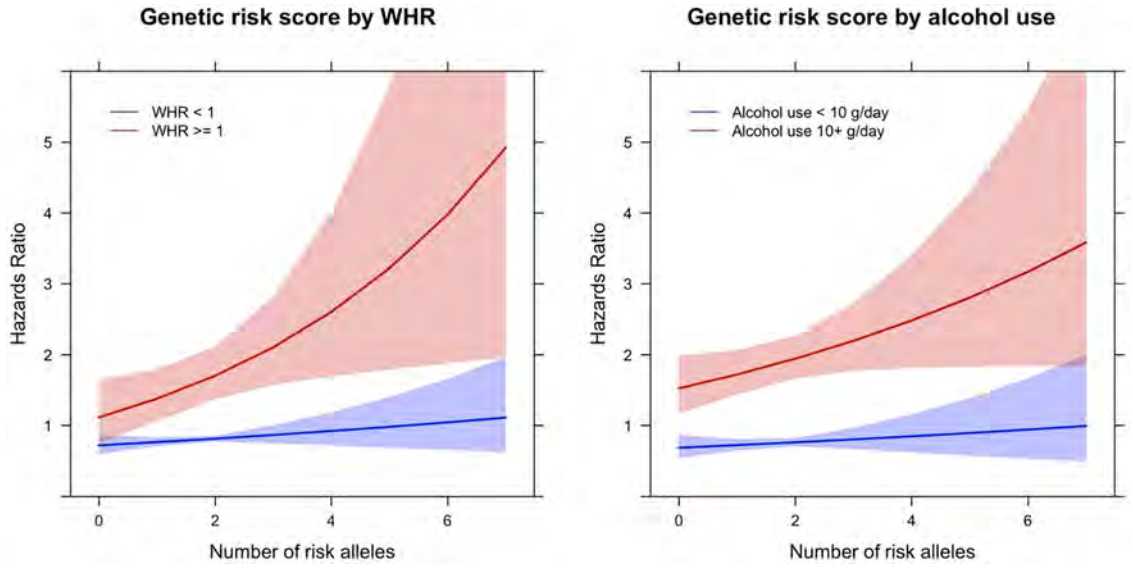

Figure: (abstract: THU044)

dependent risk increase for ILD with a 2.5-fold increase in subjects with ≥ 4 risk alleles (22% of subjects) as compared to non-carriers (14% of subjects). WHR modified this relationship, as in subjects with WHR above 1.0 (15% of subjects) the carriers of >4 risk alleles had over 3-fold higher liver disease risk as compared to non-carriers (Figure). In contrast, in subjects with WHR below 1.0 (85% of subjects), the GRS had no effect on ILD. In addition, alcohol intake modified the relationship between GRS and ILD, as in subjects drinking above 10 g/d (28% of subjects), carriers of >4 risk alleles had over 3-fold higher ILD risk compared to non-carriers (Figure). In contrast, in subjects drinking below 10 g/d (72% of subjects), the GRS had no effect on ILD.

Conclusion: The impact of several genetic variants on the risk of ILD is markedly modified by abdominal obesity and alcohol intake. Among lean abstainers and light drinkers, the common genetic risk factors do not substantially increase the risk of liver disease, which highlights the importance of lifestyle modification in prevention of advanced liver disease.

THU045

Non-alcoholic steatohepatitis is associated with liver mitochondrial DNA damage and genome instability of cytochrome b, a component of the cellular respirasome supercomplex

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Background and Aims: The progression of nonalcoholic fatty liver disease (NAFLD) into severe histological forms is paralleled by the occurrence of complex molecular processes. Damaged liver mitochondria and mitochondrial respiratory chain dysfunction are hallmark features of advanced disease. Mitochondrially encoded cytochrome B (cytochrome b, *MT-CYB*) —a member of the oxidative phosphorylation system, is a key component of the respirasome supercomplex. Here, we hypothesized that NAFLD severity is associated with liver tissue cytochrome b mutations and damaged mitochondrial DNA (mtDNA).

Method: We included 252 liver specimens of NAFLD patients–from mild to severe histological disease, which were linked to clinical and biochemical information. We sequenced the *MT-CYB* gene and we used a semi-long run real-time PCR method to detect damaged mtDNA. HPLC–mass spectrometry was used to explore circulating level of Krebs cycle metabolites in a sub-sample of patients.

Results: Compared to simple steatosis, the liver of patients with nonalcoholic steatohepatitis (NASH) exhibits a high level of *MT-CYB* sequence variation, from 12.1 to 15.6 substitutions per 10^3 bp, respectively (p = 5.5e – 10). The burden of liver *MT-CYB* variants was associated with changes in the level of metabolites, including alpha-ketoglutarate, branched-chain amino acids, glutamate, and hydroxyglutaric acid (Figure). Liver mtDNA damage at the cytochrome b region occurred more often in patients with advanced disease (p = 1e – 3) and high scores of lobular inflammation (p = 6.5e – 3). Nevertheless, the increase of damage level was a distinctive feature of patients with severe obesity (p = 7.9e – 5).

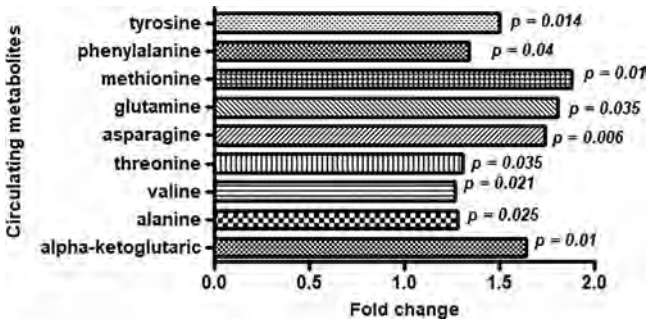

Figure: **C**hanges in the level of metabolites in NAFLD patients with a burden of more than 10 genetic variants in the *MT-CYB* with respect to those with a lower number of polymorphic sites at the locus.

Conclusion: NASH is associated with liver mtDNA damage, in particular, genetic alterations of cytochrome b, an important component of the cellular respirasome

THU046

Barriers and motivators to engaging in physical activity in individuals with NAFLD: implications for physical activity adherence

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease worldwide. In the absence of approved pharmacological agents, lifestyle modifications including physical activity (PA) and diet are the primary treatment interventions. Studies report that although individuals with NAFLD engage in less PA compared to matched controls, they understand the benefits of PA but lack the confidence to perform it. To date, there is a limited understanding of the barriers and motivators individuals with NAFLD experience in performing PA. Therefore, the objective of this study was to qualitatively assess the perceived barriers and motivators to engaging in PA in a cohort of individuals with NAFLD.

Method: 108 individuals (median age = 55 ± 15 years, 53% male) with biopsy and/or FibroScan proven NAFLD completed a series of questionnaires inclusive of the: Barriers to Becoming Active Quiz (BBAQ), Motives for Physical Activity Measure (MPAM), Rapid Assessment of Physical Activity (RAPA) questionnaire and a participant demographic questionnaire. Scores from the BBAQ and MPAM were separated into specific barrier and motivator domains. Barrier domains were further categorised as a significant barrier if a score of ≥ 5/9 was reported. Individuals were classed as physically active or inactive based on responses from the RAPA. Additionally, binary logistic regression was performed in order to assess potential predictors for self-reporting as physically active.

Results: Of the 108 individuals who completed the questionnaires, 23% correctly identified the recommended WHO PA guidelines and 41% of the population self-reported as active. Lack of willpower, lack of energy and lack of time were the most frequently cited barrier domains to engaging in PA with 59%, 40% and 39% of the sample reporting them as significant barriers, respectively. Maintaining one's health and fitness was the most cited motivator domain to engaging in PA. The regression analysis revealed that lack of willpower (OR: 1.367, 95% CI: 1.025–1.823, p = 0.033), maintaining one's health and fitness (OR: 2.421, 95% CI: 1.190–4.926, p = 0.015) and reporting ≥ three significant barriers (OR: 6.369, CI: 2.058–19.608, p = 0.001) represented significant, independent predictors of reporting as physically active.

Conclusion: This study highlights the significant barriers and motivators to engaging in PA reported by NAFLD patients and

additionally, the lack of awareness of the PA guidelines. Lack of willpower and maintaining one's health and fitness were significant predictors of individuals reporting as physically inactive which may represent areas that could be addressed to increase PA participation. Barriers and motivators to engaging in PA should be identified at the individual level to create a personalised approach for PA adherence in order to encourage lifelong adherence to the therapy.

THU047

Serious complications due to study-mandated liver biopsies in phase 3 trials for patients with advanced fibrosis due to non-alcoholic steatohepatitis

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Background and Aims: Approval of new therapies for NASH is currently based on histologic endpoints. However, liver biopsy is invasive and prone to potentially serious complications. Our aim was to describe the incidence of serious adverse events (SAEs) resulting from study-mandated liver biopsies in two phase 3 trials including patients with advanced fibrosis due to NASH.

Method: The phase 3 STELLAR trials enrolled patients with NASH and bridging fibrosis (F3, NCT03053050) or compensated cirrhosis (F4, NCT03053063) and platelets $\geq 100 \times 10^3/\mu L$. Patients underwent liver biopsy during screening to determine eligibility (in the absence of a qualifying historical biopsy) and after 48 weeks of treatment to assess the primary histological endpoint. The incidence and type of biopsy-related SAEs were described, and associations with patient characteristics (eg, demographics, diabetes mellitus, fibrosis stage, platelets, INR, MELD) and site biopsy volume (1–5, 6–12, >12 biopsies during screening) were evaluated.

Results: In total, 3955 biopsies (screening, n = 2362; on treatment, n = 1593) were performed in 2970 patients. Overall, liver biopsy-related SAEs were reported in 28 patients (screening, n = 15; on treatment, n = 13), corresponding to an incidence of 0.7% (95% CI 0.5, 1.0). All but one of these patients required hospitalization and two required blood transfusions, but no deaths were reported. SAEs due to pain, bleeding, and other complications were reported in 0.4% (95% CI 0.2, 0.6), 0.3% (95% CI 0.1, 0.5), and 0.3% (95% CI 0.2, 0.5) of biopsies, respectively. In cases with evaluable fibrosis stage, the incidence of biopsy-related SAEs was 1.2% (95% CI 0.7, 1.8) with biopsies showing cirrhosis compared with 0.4% (95% CI 0.2, 0.7) for those without cirrhosis (p = 0.004). While the incidences of bleeding (0.2% in both groups) and other complications (0.5% for cirrhosis vs 0.2% for non-cirrhosis) did not differ significantly between groups, pain was more frequent with biopsies showing cirrhosis (0.8% vs 0.1% for non-cirrhosis; p = 0.0007). No significant associations were identified between biopsy-related SAEs and other patient characteristics (age, sex, diabetes, BMI, INR, platelets, MELD) or site biopsy volume, either at screening or on treatment.

Conclusion: In these large phase 3 trials, ~1 in 140 study-mandated liver biopsies was associated with an SAE; pre-biopsy patient characteristics and site biopsy volume were not predictive of complications. Although generally safe and well tolerated, these SAEs, as well as the availability of accurate and reliable noninvasive tests (NITs), underscore the importance of transitioning towards NITs to aid patient identification and stratification, and as surrogate endpoints to evaluate treatment response in NASH clinical trials.

THU048

The burden of disease associated with non-alcoholic steatohepatitis patients under standard of care

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Background and Aims: NASH is a chronic disease that can progress to end-stage liver disease (ESLD). Patients with advanced fibrosis due to NASH are at greater risk for serious liver-related consequences, including decompensated cirrhosis (DCC) & hepatocellular carcinoma (HCC). The aim was to evaluate long-term clinical outcomes for patients with advanced fibrosis without cirrhosis due to NASH receiving current standard of care (SOC) and assess the impact of incorporating data from the simtuzumab trials.

Method: A Markov-model was developed to predict the long-term outcomes of 10,000 hypothetical NASH F3 subjects (median age 55) by following progression across all fibrosis stages and ESLD. Data from the literature on natural disease progression were applied. Firstly, from Harrison S. (2018) who reported outcomes from two simtuzumab trials [1]. Secondly, data reported by Singh S. (2015), which quantified the fibrosis progression rates based on a meta-analysis of natural history studies [2]. This allowed a comparison of outcomes with a combination of both datasets vs. outcomes with data from Singh S. only. Probabilistic sensitivity analysis was undertaken.

Results: Over lifetime, the model estimated that 79.5% & 28.2% of patients progressed to compensated cirrhosis (CC) and DCC respectively when including simtuzumab data. Alternatively, values of 74.4% & 25.1% were generated using Singh S. alone. Similarly, of the 10,000 F3 patient cohort, an additional 255 patients progressed to HCC and 120 liver transplants were estimated after including simtuzumab data. The cohort based on the simtuzumab analysis also lived shorter lives with mean total life years/patient of 14.14 years vs. 15.44 for the Singh analysis. The shorter lifespan was largely due to an increase in liver-related mortality with 49.2% of patients dying due to a liver-related event.

Conclusion: Both analyses indicate that, with SOC, people with advanced fibrosis without cirrhosis due to NASH have a substantial risk of progressing to ESLD (i.e. 30% DCC & 10% HCC respectively) over lifetime. Including simtuzumab data resulted in faster disease progression with more ESLD events predicted to occur. Compared to Singh S. only scenario based on a small numbers of F3 and CC, the analysis based on data from Harrison S. should provide a more robust long-term prediction of outcomes for NASH patients.

References

1. Harrison SA, et al. *Gastroenterology*. 2018.
2. Singh S, et al. *Clin Gastroenterol Hepatol*. 2015.

THU049

Insulin secretion is an independent predictor of hepatic ballooning in non-diabetic subjects with non-alcoholic fatty liver disease

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Background and Aims: The onset and progression of liver damage in Non-Alcoholic Fatty Liver Disease (NAFLD) is tightly associated with insulin resistance (IR) and secondary hyperinsulinaemia. Typically, NAFLD patients showed higher serum levels of both insulin and C-peptide (CP). We aimed to compare fasting IR indices based on insulin and CP and their ability to predict histological features of NASH in a cohort of non-diabetic subjects with biopsy proven NAFLD.
Method: We studied 119 subjects with histological diagnosis of NAFLD (mean age 43 y). Plasma CP was assessed by chemiluminescence assay. HOMA-IR was calculated as [(fasting glucose X fating insulin)/405]; HOMA-IR by CP was calculated replacing insulin with CP in the HOMA-IR formula; CP index (CPi), reflecting beta-cell function thus insulin secretion, was calculated as [(100*CP)/fasting glucose]. Histology was scored according to the SAF score.
Results: Insulin and CP levels significantly increased according to lobular inflammation ($p = 0.013$ and $p = 0.023$, respectively) and hepatic steatosis ($p = 0.046$ and $p = 0.026$, respectively) but only CP showed a stepwise increase according to ballooning ($p = 0.031$) and fibrosis ($p = 0.012$). HOMA-IR by insulin did not significantly increase according to the histological features of NASH while both HOMA-IR by CP and CPi were significantly higher in patients with hepatic ballooning compared to those without (0.54 ± 0.34 vs 0.35 ± 0.16, $p = 0.007$ and 2.80 ± 1.94 vs 1.82 ± 0.86, $p = 0.015$, respectively). At univariate logistic regression analysis, HOMA-IR by CP, but not HOMA-IR by insulin, was significantly associated with advanced fibrosis ($F \geq 2$) (OR = 4.1, 95% CI = 1.1–14.4, $p = 0.031$) and with the presence of ballooning (OR = 23.4, 95% CI = 2.3–233.3, $p = 0.007$). Moreover, CPi was significantly associated with the presence of ballooning (OR = 1.8, 95% CI = 1.2–2.9, $p = 0.009$). After multivariable regression analysis adjusted for the major confounding variables, BMI was significantly associated with $F \geq 2$ (OR = 1.1, 95% CI = 1.0–1.2, $p = 0.024$) while both HOMA-IR by CP and CPi were associated with the presence of ballooning (OR = 18.9, 95% CI = 1.6–217.7, $p = 0.018$ and OR = 1.7, 95% CI = 1.1–2.9, $p = 0.023$, respectively).
Conclusion: In non-diabetic patients with NAFLD, fasting IR indices derived from CP levels were closely related to hepatic ballooning suggesting the importance of insulin secretion in the onset and progression of liver disease.
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THU050

NAFLD fibrosis score identifies not only advanced liver fibrosis but also chronic vascular complications in type 2 diabetic patients

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) may silently progress to advanced fibrosis and cirrhosis in patients with type 2 diabetes (T2DM). In these patients histologic liver fibrosis as well as fibrosis detected by FibroScan® has been related to both liver-related complications and diabetic vascular complications. Since liver biopsy and FibroScan® are not easily available in routine diabetes care, we evaluated whether advanced liver fibrosis, assessed by NAFLD fibrosis score (NFS), correlates with chronic vascular complications in patients with T2DM.
Method: 394 outpatients with T2DM consecutively attending five Italian diabetes centers underwent liver ultrasonography (US) and an extensive evaluation of macro-/micro-vascular diabetic complications. In those with US-detected NAFLD, liver fibrosis was evaluated by both FibroScan® and NFS.
Results: Steatosis by US was present in 351 (89%) patients. Almost all patients (96%) were treated with hypoglycaemic drugs, 58% had at least one chronic vascular complication, 19% a macrovascular complication (myocardial infarction and/or ischemic stroke) and 32% a microvascular one (24% chronic kidney disease; 16% retinopathy; 6% peripheral neuropathy). Prevalence of advanced fibrosis assessed by either FibroScan® (LSM ≥ 8.7/7.2 kPa for the M/XL probe) or NFS (≥ 0.676) was 14% and 18% respectively, with acceptable concordance between the two methods. Prevalence of myocardial infarction and/or ischemic stroke and peripheral neuropathy was higher in patients with NFS ≥ 0.676 compared to those with NFS <0.676 (31% vs. 15%, $p = 0.007$; 19% vs. 3%, $p < 0.001$). NFS was significantly associated with cardiovascular events and peripheral neuropathy (adjusted-OR 2.2, 95%CI 1.0–4.9; $p = 0.05$ and adjusted-OR 5.5, 95%CI 1.7–18.4; $p = 0.005$, respectively), even after adjustment for centre, sex, smoking, haemoglobin A1c, duration of diabetes, hypertension and use of statins or ACE-I/ARBs (age and BMI were not also adjusted for because they were included in the NFS). Similarly, FibroScan®-measured LSM was also independently associated with cardiovascular complications and peripheral neuropathy.
Conclusion: The NFS, which is an easy and affordable non-invasive test of advanced liver fibrosis, may help clinicians in primary care in identifying patients with T2DM and NAFLD at higher risk of having both hepatic and chronic vascular complications, possibly applying more intensive preventive and therapeutic strategies.

THU052

Clinical and economic impact of non-alcoholic fatty liver disease in Spain

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Background and Aims: NAFLD/NASH is a growing concern due to its increased prevalence and incidence in Spain. However, Spain specific data is lacking. This study aims to determine the clinical (progression of fibrosis) and economic (resource use and health costs) consequences of non-alcoholic fatty liver in usual clinical practice in Spain.
Method: Observational, retrospective study based on the review of medical records of patients aged ≥ 18 years who required care in 2017–2018. According to the stage of fibrosis (calculation method: FIB-4), patients were classified into 2 groups: a) F0–F2 and b) F3–F4

(advanced fibrosis). The follow-up was 1 year. Main measures: comorbidity, concomitant medication and resource use and costs. The results were analyzed using multivariate analysis, with a value of $p < 0.05$ considered significant.

Results: 8,151 patients were recruited with a mean age of 61.1 years and 51.5% were male. By groups: a) mild fibrosis n = 7,127 (87.4%) and b) advanced fibrosis n = 1,024 (12.6%; 6.8% with liver cirrhosis). The most frequent comorbidities were dyslipidemia (63%), obesity (52%), hypertension (52%) and diabetes (35%). There was a mean of 2.1 medications per patient. Patients with advanced fibrosis (F3–F4) had a higher mean concomitant medication (2.5 vs. 2.1; $p < 0.001$) and AST/ALT ratio (1.1 vs. 0.8; $p < 0.001$). The mean cost (patient-year) of subjects with advanced fibrosis corrected by covariates was higher (€ 1,812 vs. € 1,128, $p < 0.001$). Patients with diabetes were older and had higher morbidity, concomitant medication, fibrosis stage and total costs.

Conclusion: Patients with advanced fibrosis were associated with high level of comorbidity and concomitant medication, resulting in high health costs for the Spanish National Health System. Patients with diabetes have more comorbidities and severe liver disease, impacting on the costs.

THU053

Europe's largest meta-analysis on the prevalence of non-alcoholic fatty liver disease, non-alcoholic steatohepatitis and advanced fibrosis (F3-F4)

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Background and Aims: The increasing prevalence of nonalcoholic fatty liver disease (NAFLD) fuelled by obesity and diabetes epidemics has become a significant health burden. Information on the prevalence of the disease across Europe is limited. Previous systematic reviews focused on scarce data published up to 2015. Our aim was to estimate the European prevalence of NAFLD, nonalcoholic steatohepatitis (NASH), and advanced fibrosis (stage F3–F4) from more recently published data.

Method: A systematic review identifying observational studies with data on NAFLD, NASH and advanced fibrosis prevalence conducted in Europe was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed was searched for studies published until October 2019. Strict exclusion criteria were applied to eliminate the effect of confounding factors on prevalence estimates. Studies on individuals with alcohol abuse, on liver disease patients related to other etiologies, and studies exclusively enrolling morbidly obese and diabetic patients were

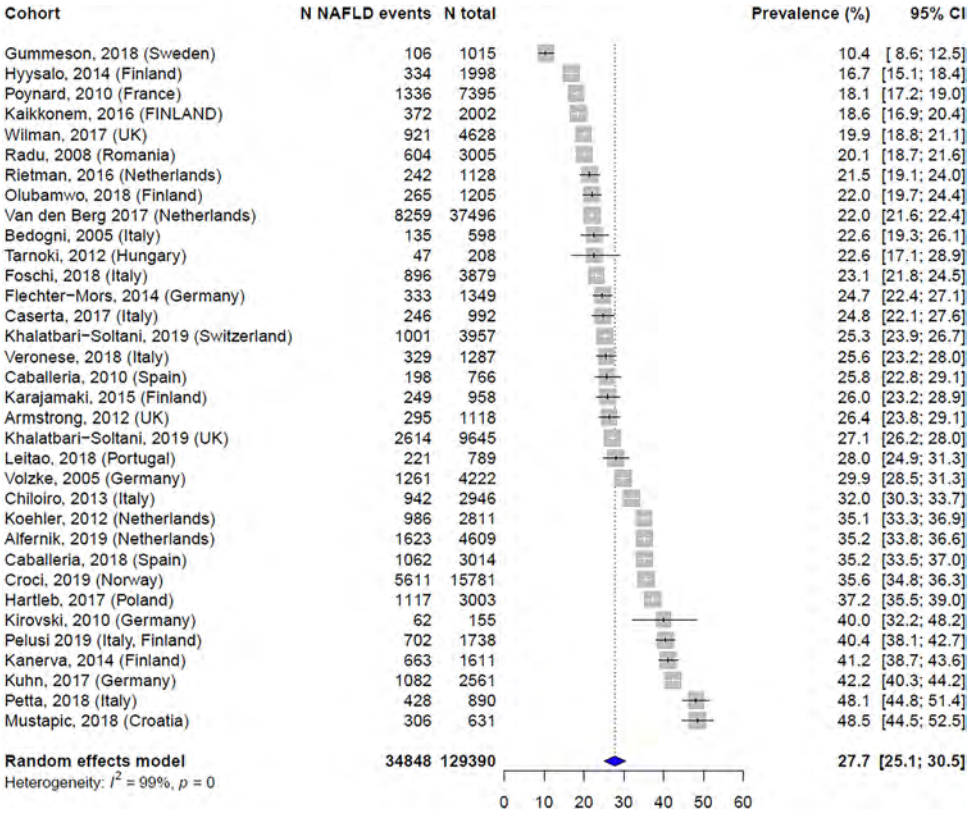

Figure: (abstract: THU053): Forest plot of NAFLD prevalence in European studies.

excluded. We used random effects model meta-analysis to estimate prevalence (95% confidence interval [CI]).
Results: Out of 588 studies identified, 33 studies from 15 European countries met the inclusion criteria comprising 129,390 individuals (>18 years old), of whom 34,848 had NAFLD. The overall NAFLD prevalence estimated in the random effects meta-analysis model was 27.7% (95% CI 25.1–30.5) [Fig. 1]. An estimated 64.1% (95% CI 51.4–75.0) of the biopsy-proven 4,696 NAFLD patients (12 studies) had NASH. Ten studies reported information regarding advanced fibrosis among NAFLD patients. The overall advanced fibrosis prevalence among these patients was 12.8% (95% CI 9.8–16.5). Subgroup meta-analyses by age group, sex, and diagnostic method as well as meta-regression analyses to investigate heterogeneity are ongoing and will be reported.
Conclusion: To our knowledge this is the largest meta-analysis to date providing an overview of the burden of NAFLD, NASH and advanced fibrosis in Europe. These data add to the evidence base and may be particularly useful in European settings that currently lack data.

THU054

Patients receiving liver transplant for NASH cirrhosis have greater muscle loss compared to transplant and non-transplant control

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Background and Aims: Skeletal muscle loss is common in patients with cirrhosis and associated with increased morbidity and mortality following liver transplantation (LT). Since most patients receiving LT in the 5th and 6th decade of life, it is unclear if the muscle loss seen after LT is age related or specifically due to LT. Furthermore, NASH, a rapidly growing indication for LT, is associated with pre-LT muscle loss even in the absence of cirrhosis and it is unclear if this worsens following LT. Thus, to overcome these significant limitations we conducted the following prospective study to better define the impact of LT and NASH on skeletal muscle loss and body compartments.
Method: Adult LT recipients (N = 21) were prospectively enrolled at author's institution and underwent body composition MRI. Patients with active malignancy, heart failure, ESRD on dialysis, multi-visceral transplant and rejection within 6 months of enrolment were excluded. Body compartments quantified included: visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), muscle volume, fat free muscle volume (FFMV), muscle fat infiltration (MFI). All these measurements were subsequently standardized to patient height (i.e. VATi, SATi, FFMVi, etc.). To determine the impact of LT on body compartments, LT recipients were matched 1:150 to virtual control group (VCG) from UK imaging biobank with regards to age, gender, and body mass index (BMI) and the data is reported as the number of standard deviations (SD) from the mean of the VCG. The analysis then was stratified to LT for NASH vs. non-NASH etiologies of cirrhosis.
Results: The study included 21 patients (n = 11 for NASH and n = 10 for non-NASH), mean age 61 ± 11 years and mean BMI 32 ± 7 kg/m^2. The subjects with NASH were more likely to have cardiometabolic disease such as obesity, diabetes and dyslipidemia (P < 0.01 for NASH vs. non-NASH). The median time from LT was 2 (IQR 1, 7) years. Compared to VCG, patients transplanted for NASH cirrhosis had higher VATi (3.23 vs. 2.52; P < 0.01) and lower FFMVi (−0.98 vs. 0.03, P = 0.016). (Figure 1) Patients transplanted for non-NASH cirrhosis had similar VATi and FFMVi when compared to VCG cohort. Interestingly, in LT recipients patients transplanted for NASH cirrhosis were likely to have higher VATi (3.23 vs. 0.85; P = 0.01), SATi (5.23 vs. 2.63; P < 0.01), MFI (3.33% vs. −1.92; P = 0.02). In correlative analysis, post-LT factors associated with reduced FFMVi were increased BMI. Similarly, diabetes and increased BMI were associated with FMI in LT recipients.
Conclusion: LT recipients, particularly, those transplanted for NASH cirrhosis are at elevated risk of skeletal muscle loss, which correlates with cardiometabolic risk. This decrease in muscle mass and increase adiposity (i.e. sarcopenic obesity) likely contributes to increased cardiometabolic morbidity and mortality in LT.

THU055

A national cross-sectional survey of health-related quality of life in Chinese patients with non-alcoholic fatty liver disease

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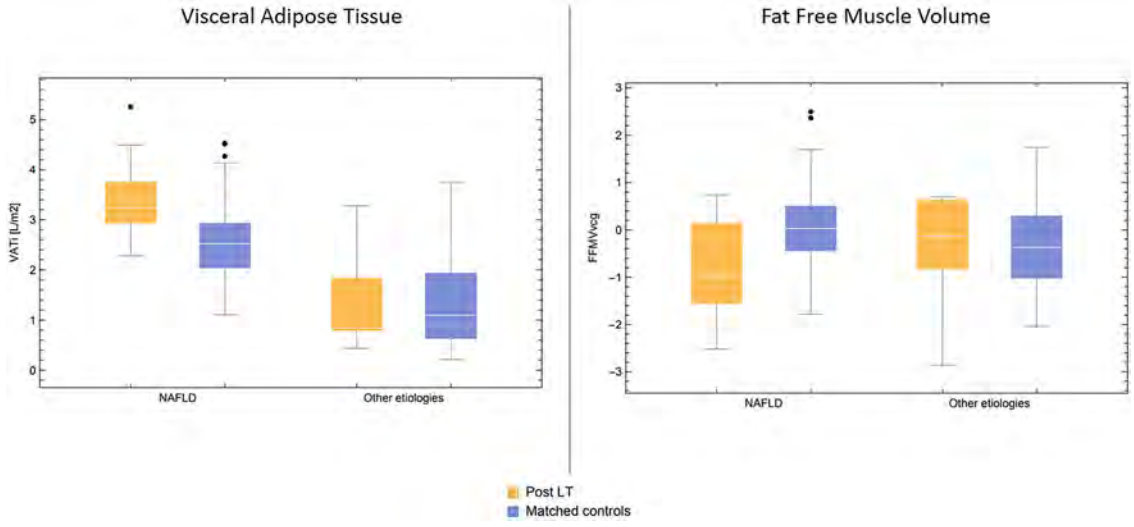

Figure: (abstract: THU054)

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are the most common causes of chronic liver disease with known negative impact on patients' health-related quality of life (HROQL). Our aim was to assess the impact of NAFLD on Chinese patients' HRQOL.
Method: In this national cross-sectional survey, patients with NAFLD in absence of other liver disease were identified between March 1st to August 1st 2019. Chronic Liver Disease Questionnaire-Non-Alcoholic Fatty Liver Disease (CLDQ-NAFLD) were used to qualify HRQOL. Logistic regression analysis was performed to identify risk factors of HRQOL by CLDQ-NAFLD.
Results: 5181 NAFLD patients from 90 hospitals among China were included into the analysis (Figure). The mean age was 43.79 ± 13.29 years and 55% were males. 46% were obese. 4%, 0.5% of patients reported a history of NASH or cirrhosis. The mean AST and triglyceride (TG) were 39.9 ± 37.9 U/L and 2.44 ± 2.14 mmon/L. The overall CLDQ-NAFLD score was 5.66 ± 0.89. NAFLD patients had impaired HRQOL in all domains of CLDQ-NAFLD (abdominal symptoms, 5.59 ± 1.07; activity, 5.73 ± 0.95; emotions, 5.66 ± 0.98; fatigue, 5.31 ± 1.10; systemic symptoms, 5.31 ± 1.10; worry, 5.88 ± 1.00). Males were more worried than females (5.84 ± 1.00 & 5.95 ± 1.01, p = 0.000). The young were more worried than the old (p = 0.019), but the old had more difficulty of activity (p = 0.006) and more systemic symptoms (p = 0.000). Besides, some other social characteristics impacted HRQOL in both overall score and all domains (region, p = 0.000; education, p = 0.000; income, p = 0.000). Obesity (p = 0.000) and complications (ex. diabetes, hypertension, hyperlipidemia) (p = 0.000) impacted HRQOL a lot in all domains. Patients with more severe liver disease had significantly lower overall scores (simple fatty liver, 5.67 ± 0.87; NASH, 5.17 ± 1.00; 4.79 ± 1.02, p = 0.000). Logistic regression indicated that obesity, disease progression, cardiovascular diseases, ALT and TG were independent risk factors on the overall score of CLDQ-NAFLD. In the logistic analyses of individual domain, obesity and TG were independent risk factors of all the six domains. ALT and CVD impacted five domains of CLDQ-NAFLD.
Conclusion: In this national cross-sectional survey of NAFLD patients in China, we indicated HRQOL of Chinese NAFLD patients. Significant negative associations between HRQOL and clinical factors such as obesity, disease progression, cardiovascular diseases, ALT and TG emerged. We have to focus on optimally managing care of NAFLD patients and improving their HRQOL.

THU056

Risk factors associated with subclinical atherosclerosis in the patients with biopsy-proven non-alcoholic fatty liver disease

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Background and Aims: The association between the progress of nonalcoholic fatty liver disease (NAFLD) and subclinical atherosclerosis remains controversial. This study aimed to clarify the factors related to subclinical arteriosclerosis, including the histopathological severity of the disease and PNPLA3 gene polymorphisms, in NAFLD patients.
Method: We measured brachial-ankle pulse wave velocity (baPWV) and maximum intima-media thickness (max-IMT) as an index of subclinical arteriosclerosis in 153 biopsy-proven NAFLD patients. Referring to previous reports, patients with baPWV ≥ 1600 cm/s or max-IMT ≥ 1.1 mm were defined as a risk group for cardiovascular events.
Results: The baPWV and max-IMT values were significantly higher in the advanced fibrosis group than in the less advanced group (baPWV: median, 1679 cm/s vs 1489 cm/s; $p = 5.49 \times 10^{-4}$, max-IMT: 1.2 mm vs 1.0 mm; $p = 3.14 \times 10^{-2}$). Multiple logistic regression analysis revealed that older age, hypertension, and advanced fibrosis were independently linked to baPWV ≥ 1600 cm/s. On the other hand, older age, male and diabetes were independent factors related to max-IMT ≥ 1.1 mm. NAFLD patients were categorized into low-risk group (number of risk factors = 0), intermediate-risk group (= 1), and high-risk group (≥ 2) based on their risk factors (baPWV: risk factors including older age, hypertension, and advanced fibrosis, max-IMT: risk factors including older age, male and diabetes). The prevalence of baPWV ≥ 1600 cm/s was 7.1% (3/42) in the low-risk group, 30.8% (12/39) in the intermediate-risk group, and 63.9% (46/72) in the high-risk group. The prevalence of max-IMT ≥ 1.1 mm was 8.9% (4/45) in the low-risk group, 31.8% (14/44) in the intermediate-risk group, and 51.6% (33/64) in the high-risk group.
Conclusion: We identified factors associated with subclinical arteriosclerosis in NAFLD patients assessed by baPWV and max-IMT, respectively. The differences in the factors associated with baPWV and max-IMT may indicate the need to consider the appropriate use of these two methods for evaluating subclinical arteriosclerosis in NAFLD patients.

THU057
Progression of non-alcoholic fatty liver disease is rare in a Danish tertiary liver centre
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Background and Aims: Data concerning non-invasive discrimination of simple steatosis from non-alcoholic steatohepatitis (NASH) patients and the prediction of risk of disease progression in patients with non-alcoholic fatty liver disease (NAFLD) are conflicting. We aimed to investigate these factors in a NAFLD cohort at a Danish tertiary liver centre.
Method: We retrospectively assessed 135 patients with biopsy-proven NAFLD between 2008–2018 and followed them to the end of 2018 via their electronic patient charts. Patients were divided according to the presence of simple steatosis or NASH based on the steatosis, activity, and fibrosis (SAF) score and the NAFLD activity score (NAS) in liver biopsies. Histological and clinical progression were assessed during follow-up.
Results: NASH patients had higher BMI, liver stiffness, HbA1c, sCD163, and were more prone to have metabolic syndrome at baseline compared with simple steatosis patients. Of the 135 patients, 31 had a follow-up biopsy after a median of 287 days (range: 172 days – 25.5 years); simple steatosis progressed to NASH in 7/25 (28%) cases, and 2/6 (33%) regressed from NASH to simple steatosis. Twenty patients (65%) had the same fibrosis stage on the follow-up biopsy, 7 (23%) progressed, and 4 (13%) regressed. Only 14 (10%) patients progressed clinically during a median follow-up time of 3.8 years (range: 12 days – 27 years) and this mainly included developing type 2 diabetes mellitus (n = 10, 7%). Clinical progression was associated with female sex, and high creatinine, fibrosis stage, activity score, and ballooning in the diagnostic liver biopsies.
Conclusion: The NASH patients separated from simple steatosis patients on several components at baseline including the metabolic syndrome. Histological progression was observed in several patients while some regressed. Only 10% progressed with a clinical event during follow-up, mainly related to more severe histological disease at baseline.

THU058
Health-care burden of NAFLD in European hospital-based outpatient hepatology clinics: real-world prospective data from the CONSTANS study
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Background and Aims: In Europe data on the burden of NAFLD in a real-life setting in outpatient hepatology clinics is lacking.
Method: Prospective observational study of pts attending the outpatient hepatology clinic during a 3 month period in 9 centers from 8 European countries. Suspected NAFLD was defined as referrals for steatosis, increased LFTs, hyperferritinemia or cryptogenic cirrhosis. Suspected or already confirmed NAFLD were included in a 6–12 months follow-up study which recorded the final diagnosis, severity of the disease, diagnostic/monitoring work-up and cost of use of medical procedures
Results: 5240 patients were included (N) in Germany (1973), Switzerland (914), France (848), UK (694), Italy (470), Spain (191) and Slovakia (150). The main reasons for referral were: NAFLD 24.8% (including 13.1% suspected NAFLD and 11.7% known NAFLD), viral hepatitis 33.6%, alcoholic liver disease 9.1%, gastrointestinal cancers or cholangiocarcinoma 2.5% and hepatocellular carcinoma or other causes of chronic liver disease 30%. During 7 ± 3.7 months f/u 237 pts underwent liver biopsy. NAFLD was confirmed in 76% (NASH in 54% and NASH cirrhosis in 4.6%) and cryptogenic cirrhosis in 3.8%. In pts without biopsy NAFLD was confirmed in 77% (10% with NASH cirrhosis), NAFLD+moderate alcohol in 6.5% and cryptogenic cirrhosis in 2%. Overall, fibrosis stage 2–4 was diagnosed in 62% of biopsied pts and 40% of adjudicated, non-biopsied pts.
There were 1.5 ± 1.5 f/u visits per pt. Blood tests were performed in 87% of pts and 48% had a diagnostic work-up for other CLD. Imaging was performed in 55% of pts (64% US, 6% CT scan, 7% MRI), serum fibrosis markers in 37% and transient elastography in 36%. 11% of pts were hospitalized for diagnostic procedures. Pharmacological therapy (mainly UDCA and Vitamin E) was prescribed in 9% of pts. Only 18% of pts were referred to a specialist for comorbidities. Overall and per country cost analyses will be provided

%	FR	GR	IT	UK	SK	CH	SP
NAFLD referral	39	17	39	25	47	16	35
Liver biopsy	3.4	4.6	4.9	0.7	0	1.5	0
Fibroscan use	52	38	70	29	0	86	12
Fibrosis biomarkers	61	53	54	0	0	1.4	7

Conclusion: In a large, prospective, European real-life study of tertiary care outpatient hepatology clinics, 25% of pts are currently referred for known or suspected NAFLD which is confirmed in 77% of cases after multiple diagnostic procedures. 40–62% have advanced fibrosis and 8.4–12% cirrhosis. Diagnostic practices vary widely between countries and pt referral for comorbidities is low. NAFLD is becoming a major burden on hepatology outpatient clinics in Europe

THU059

Factors associated with increased overall and cause-specific mortality in non-alcoholic fatty liver disease in an ethnically diverse cohort in the United States

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) has become the most prevalent chronic liver disease worldwide. We aimed to determine the overall and cause-specific mortality of NAFLD and identify factors associated with mortality in African Americans, Japanese Americans, Latinos, Native Hawaiians, and whites in a population-based Multiethnic Cohort Study.
Method: We conducted a prospective analysis with 2,201 participants with NAFLD (426 with cirrhosis) and 21,545 matched controls. Demographic and risk factor data were collected via baseline and updated using follow-up questionnaires. Deaths were determined through linkage to state death certificate files and the National Death Index. Cox models with covariate adjustment were utilized to calculate hazard ratios (HR) and 95% confidence interval (CI). We determined the association with overall, cardiovascular disease (CVD), non-liver cancer, and liver related mortality.
Results: After an average follow-up of 5.4 years, 582 persons with NAFLD and 3,898 controls died. The most common cause of death in NAFLD was CVD (32%), followed by cancer (22%) and liver disease (9%). After adjusting for age, sex, education, race/ethnicity, body mass index, diabetes mellitus, smoking status, alcohol intake, physical activity and history of cancer or CVD, NAFLD was associated with higher overall (HR = 1.78; 95% CI: 1.61, 1.97), CVD (HR = 1.54; 95% CI: 1.29, 1.83), non-liver cancer (HR = 1.74; 95% CI: 1.41, 2.15), and liver cancer (HR = 17.5; 95% CI: 7.00, 43.7) mortality. The mortality risk associated with NAFLD is highest in African Americans (HR = 3.20; 95% CI: 2.32, 4.41), followed by Latinos (HR = 2.69; 95% CI: 2.19, 3.31), whites (HR = 1.99; 95% CI: 1.57, 2.52), Native Hawaiians (HR = 1.35; 95% CI: 0.89, 2.06) and lowest in Japanese Americans (HR = 1.29; 95% CI: 1.10, 1.51); males and NAFLD with cirrhosis also have elevated overall mortality risk. Among NAFLD patients, factors associated with increased overall mortality were cirrhosis status, being African American, diabetes, smoking, history of CVD; while being female or Japanese American were associated with reduced mortality risk. For CVD mortality, NAFLD with cirrhosis, African Americans, diabetes, and history of CVD had increased risk; while females and moderate alcohol drinkers had lower risk. For non-liver cancer mortality, cirrhosis, diabetes, smoking, moderate alcohol drinking and history of cancer were associated with increased risk. For liver cancer mortality, having cirrhosis and diabetes were associated with increased risk.
Conclusion: In this large multiethnic cohort with comprehensive risk factor data, NAFLD was independently associated with higher overall, CVD, non-liver cancer, and liver cancer mortality. Several factors including sex, race/ethnicity, diabetes, comorbid conditions and lifestyle factors influence mortality in participants with NAFLD.

THU060

First 1-year follow up data from the German NAFLD prospective real-life cohort (FLAG study) show low frequencies of lifestyle changes

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Background and Aims: Nonalcoholic fatty liver disease (NAFLD) affects approximately 25% of the German population. However, there is only limited knowledge about the prevalence of NAFLD with advanced fibrosis, the frequencies of lifestyle interventions (e.g. nutritional counselling) over time and their effect on body weight loss and liver function tests. Cohort studies in a "real life" setting represent a suitable tool to study clinical outcomes in patients with NAFLD and assess current standards of health care.
Method: The fatty liver assessment in Germany (FLAG) study is a prospective, multicentric cohort study initiated by the association of gastroenterologists in private practice (BNG) in cooperation with academic medical centers and the German Liver Foundation covering secondary and tertiary health care levels. Data collection is performed using an electronic case report form, and data quality is verified by plausibility checks and off-site monitoring. Patients characteristics as well as laboratory parameters that allow calculation of non-commercial, non-invasive liver fibrosis scores and genetic profiles are collected. Liver stiffness measurement (LSM) data are included when available. Lifestyle interventions, medication as well as clinical events are assessed at baseline and followed-up prospectively.
Results: Today, 674 patients with NAFLD spanning a broad range of disease severity are included in the FLAG study. Baseline data were reported previously, including 52% men with a mean age of 52 years. According to FIB-4 index, 7% of the patients have significant fibrosis (F3-F4, Fib-4-Index >3.25). Here, we report 1-year follow up (FU) data from the first 115 patients. Total body weight increased in 48/115 patients (42%). Highest weight loss of >5% total body weight was observed in 19/115 (17%) of patients. In those with the highest weight loss, ALT activities (U/L) decreased significantly ($p < 0.01$) over time (mean ± SD, 70 ± 44 vs. 39 ± 23 at baseline vs. 1-year FU, respectively). HbA1c values (mg%) decreased numerically (mean ± SD, 6.1 ± 1.0 vs. 5.8 ± 0.4, $p > 0.05$). In patients who gained weight, ALT levels at baseline and during FU (57 ± 28 vs. 71 ± 48 U/L, $p = 0.08$) and HbA1c values (5.90 ± 0.70 vs. 5.91 ± 0.77 mg%) showed a slight increase or remained unchanged, respectively. Nutritional counselling was performed in 23% of all patients only, however, its frequency did not differ between groups.

Conclusion: In this prospective, multicentric cohort study, first 1-year FU data of patients with NAFLD provide insights in real life patient care in Germany. Weight loss was associated with a significant decrease of ALT levels, however, only 17% of all patients showed a weight loss of >5% total body weight after the first year of FU. The results underscore that lifestyle interventions such as nutritional counselling are limited and should be strengthened.

THU061

Fibrosis non-invasive tests capture changes in patient-reported outcomes of patients with advanced non-alcoholic steatohepatitis

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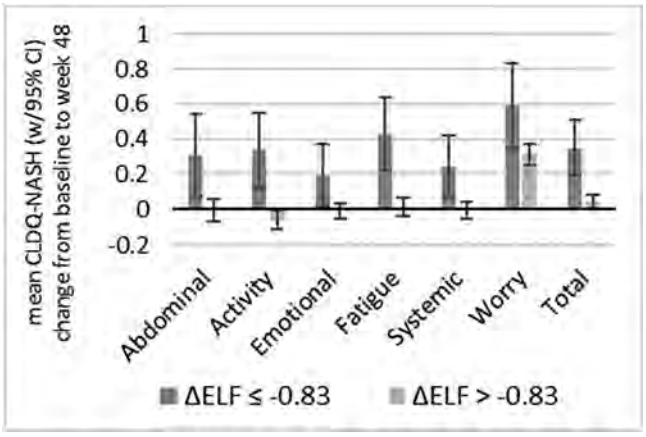
Background and Aims: Non-alcoholic steatohepatitis (NASH) can impair health-related quality of life and other patient-reported outcomes (PROs) which can be further impacted by histologic fibrosis stage or noninvasive tests (NITs) for fibrosis.
Method: Patients with NASH (NAS ≥ 3) and advanced fibrosis (NASH CRN stage F3) or compensated cirrhosis (CC, F4) were enrolled in two Phase 3 clinical trials of selonsertib (STELLAR). PROs were prospectively collected using SF-36, CLDQ-NASH, EQ-5D, and WPAI at pre-treatment baseline and during treatment. Liver biopsies were collected at baseline and week 48. The trials were terminated after week 48 due to the lack of efficacy of selonsertib.
Results: A total of 1,679 patients with biopsy-proven NASH were included (802 F3 and 877 CC, 40% male, 74% white, 49% employed, 74% with diabetes, 42% history of psychiatric comorbidities). Compared with NASH patients with F3 fibrosis, NASH-CC patients were more frequently female, white, had more gastrointestinal and psychiatric comorbidities, and a higher prevalence of diabetes (77% vs. 70%) (all $p < 0.05$). At baseline, NASH-CC patients had lower scores in Role Physical, Bodily Pain, and Social Functioning of SF-36, EQ-5Q utility, and all but one domains of CLDQ-NASH ($p < 0.05$). In multivariate analysis adjusted for demographics, BMI, and comorbidities, the presence of CC was independently associated with lower scores in the domains of Activity, Emotional, and Worry of CLDQ-NASH ($p < 0.05$). Patients who improved histologic fibrosis stage after 48 weeks were more likely to have histologic cirrhosis at baseline (58% vs. 50%, $p = 0.02$) but otherwise had less active disease [lower ballooning stage, less diabetes, lower AST, higher platelet count and albumin, lower CRP and GGT, better fibrosis NIT scores such as APRI, FIB-4, Fibrotest, ELF, Hepamet, NAFLD Fibrosis Score, and liver stiffness by transient elastography (LS by TE) (all $p < 0.01$). Achieving ≥ 1 stage histologic fibrosis improvement (without or regardless of worsening of NASH) was not associated with any improvement in PROs (all $p > 0.05$). Patients with a decrease in % collagen (absolute ≥ 0.9 percentage points or relative ≥ 14% from baseline) experienced improvement in General Health scores ($p < 0.05$). In addition, patients with decreases in NAS score (≥ 2 points), LS by TE (≥ 4.6 kPa), and ELF score (≥ 0.83 points) experienced improvement of scores in most domains of CLDQ-NASH ($p < 0.05$) (Figure).



Conclusion: In addition to baseline impairment associated with the disease severity in patients with advanced NASH, there was association of NIT improvement with PRO improvement.

Alcoholic liver disease

THU062

Gut transcriptomics reveals potential therapeutic strategies for the restoration of epithelial barrier repair in alcohol-related liver cirrhosis

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Background and Aims: Liver cirrhosis induces a profound state of immunodeficiency, rendering patients highly susceptible to bacterial infection and increased mortality. We have previously shown that gut hyperpermeability and consequent increased bacterial translocation are central in driving this phenomenon in Alcohol-related Liver Disease (ALD) (Riva et al, Gut 2018; Markwick et al, *Gastroenterology* 2015); however, the specific pathways associated with intestinal damage in ALD are not well characterised.
Method: Genome-wide transcriptome profiling (~20,000 coding genes, ~40,000 long non-coding RNA) was performed in colon tissue from 10 alcohol-cirrhotic patients (ARC; F = 5, age = 57.2 ± 1.7, MELD = 12.7 ± 1.3, lactulose = 4, no alcoholic hepatitis/infections/antibiotics) and 10 healthy controls (HC; F = 1, age = 52.2 ± 2.5). We investigated differential gene expression and functional clustering by "Gene Ontology" (GO), "Kyoto Encyclopaedia of Genes and Genomes" (KEGG) pathways and "Gene Set Enrichment Analysis" (GSEA). We also measured surrogate markers of bacterial translocation (D-Lactate, Endotoxin) as indicative of gut barrier disruption in ARC patients.
Results: ~8,400 coding genes were differentially expressed in ARC vs HC colon. Most upregulated genes were functionally involved in transcriptional processes, ribosomal/chromatin structure, intercellular adhesion and energy metabolism. GSEA identified upregulated cell adhesion pathways in ARC vs HC, driven by tight and adherens

junction (TJ/AJ) genes including claudin 3, occludin, ZO-1, E/LI-cadherin and catenins. Differential expression of TJ/AJ-modulating long non-coding RNAs was consistent with the observed transcriptional changes in coding genes. Interestingly, downregulated gene clusters did not achieve significant enrichment. Quantification of plasma D-Lactate and endotoxin (Lps) confirmed the presence of bacterial translocation in ARC vs HC.
Conclusion: In conclusion, transcriptional profiling highlights major alterations in intestinal cell adhesion pathways in ALD patients suggestive of active ongoing barrier protection and epithelial repair. Further research investigating these pathways in experimental models as new targets to restore barrier integrity in ALD is warranted.

THU063
Specific alterations of the immune checkpoint secretome are linked with antibacterial immunity in alcohol-related liver disease
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Background and Aims: Alcohol-related liver disease (ALD) is characterised by a hyperinflammatory state that co-exists with profound immunoparesis. Checkpoint receptors (CR) are key regulators of immunity and we have shown a role for two inhibitory T-cell CRs (PD1/TIM3) expressed on the membrane (m) of antibacterial T cells in patients with acute alcoholic hepatitis (AH), which when neutralised in-vitro can rescue antibacterial responses (Markwick et al, 2015). However, individual roles of PD1 and TIM3 in driving immune derangements remain unclear. Recent evidence has also revealed that soluble (s) forms of CRs can in many contexts modulate autoimmunity and responses to infection/malignancy. Their role in ALD is unknown.
Method: In 22 patients with alcohol-related cirrhosis (ARC), 13 with AH and 13 healthy controls (HC) we measured PD1/TIM3 and their ligands on the membrane of immune cells by flow cytometry and as soluble forms in plasma by ELISA. CR gene expression was assessed by gene microarray. In addition, we explored the kinetics and relationship between sCRs and mCRs in *E. coli*-challenged PBMCs. Finally, rescue of antibacterial responses by neutralisation of CRs was investigated in-vitro.
Results: Plasma levels of sTIM3 were increased in ALD vs HC ($p = 0.00002$), and hyperexpression of mTIM3, mPD1 and mPDL2 was detected on ALD PBMC vs HC (AH > ARC; $p < 0.002$). Multivariate analysis revealed sTIM3 as (a) the dominant plasma sCR in ALD, (b) the strongest patient discriminator by AUROC and OPLS-DA, and (c) the only sCR directly correlated to gene expression. TIM3 ligands galectin 9 (sGal9) and sCEACAM1 were also increased in ALD vs HC (AH > ARC; $p < 0.002$). Upon *E. coli* challenge mCR expression changed comparably in ALD and HC PBMCs, and in-vitro neutralisation of TIM3 pathway led to enhanced antibacterial cytokine production (IFNγ/IL-17) and antinflammatory cytokine production (IL-10) in AH.
Conclusion: In conclusion, sTIM3 is hyper-secreted in ALD patients, particularly those with greater disease severity, in correlation with inhibitory mTIM3 expression on ALD immune cells. Blockade of the TIM3-ligand synapse restores antibacterial immunity and increases the production of antinflammatory cytokines, revealing TIM3 as a key checkpoint receptor mediating hyperinflammatory immunodeficiency in AH. Anti-TIM3 therapy is currently being used in Phase I clinical trials for advanced solid tumours and warrants further investigation as an immunomodulatory therapeutic strategy for ALD.

THU064
Proton pump inhibitors increase the risk of oral cancer among patients with alcoholic cirrhosis
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Background and Aims: Proton pump inhibitors (PPIs) increase risk of complications in patients with liver cirrhosis, most likely caused by alterations in the gut and oral microbiome. The risk of oral cancer is increased by alcohol intake and smoking, but oral microbiome alterations have also been suggested as a risk factor. We aimed to examine the association between PPI use and the risk of oral cancer among patients with alcoholic cirrhosis.
Method: We conducted a registry-based Danish nationwide historical cohort study including 17,632 patients diagnosed with alcoholic cirrhosis between 2000 and 2017. Follow-up started on the date of alcoholic cirrhosis diagnosis, and ended at diagnosis of oral cancer, death or 31 December 2017, whichever occurred first. We collected data on PPI use from the Danish National Prescription Registry. We used Cox regression to estimate the hazard ratio (HR) of oral cancer in PPI users vs. non-users adjusting for confounding by gender, age, calendar year, severity of alcoholic cirrhosis and smoking. PPI use was set as a time-dependent exposure. We examined the association between PPI use and pharyngeal cancer with identical methods.
Results: At inclusion, 4,302 patients (24%) used PPIs, and 15,357 patients (87%) used PPIs at some point. Of the study population, 12,002 patients (68%) were male, the median age at inclusion was 58.5 years (IQR 51.1–65.2) and 5,800 patients (33%) were smokers. At inclusion, 6,668 patients (38%) had a history of ascites, and 1,806 patients (10%) had a history of variceal bleeding. Oral cancer was diagnosed in 131 patients, and 12,121 patients died during follow-up. The 10-year cumulative risk of oral cancer was 0.98% (0.66–1.42) among baseline PPI users vs. 0.89% (0.72–1.09) among baseline nonusers. PPI users had a higher rate of oral cancer than non-users (adjusted HR = 1.79, 95% CI 1.21–2.65), but PPI users did not have a higher mortality than non-users (adjusted HR = 1.04, 95% CI 0.99–1.08). PPI use did not increase the risk of pharyngeal cancer (adjusted HR = 1.06, 95% CI 0.75–1.50).
Conclusion: PPIs are widely used among patients with alcoholic cirrhosis. PPI use increased the risk of oral cancer, but the 10-year risk of oral cancer was low. These findings call for further investigation of the links between PPI use, oral microbiome and cancer development.

THU065
Analysis of the influence of alcoholic abstinence on mortality in patients with alcoholic liver cirrhosis
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Background and Aims: Alcohol abstinence (AA) is the main treatment of alcoholic liver cirrhosis (ALC) but there are few data about its influence on mortality. The aim was to know if AA reduces the risk of death in patients with ALC.
Method: 754 patients with ALC, Child A/B, included in a hepatocellular carcinoma surveillance programme prospectively followed biannually. AA was defined as absence of any consumption from

inclusion. Any death after liver transplant (LT) was considered liver-related mortality (LRM). 83% males, median age 56 years, 64% with previous liver decompensation, 77% Child A, 75% with varices. 14 variables collected at inclusion were analyzed together with AA during follow-up.
Results: During 72 months (33–119), 368 patients (49%) remained abstinent, 350 (46%) died and 70 (9%) received a LT. 207 (59%) were LR deaths, 125 (36%) non LR and 18 of unknown etiology. Any cause mortality (ACM) at 5, 10 and 20 years was 24%, 45% and 77%. Age (HR:1.042;CI95%:1.026–1.059), male sex (HR:1.665;CI95%:1,.06–2.301), BMI<25 (HR:1.951;CI95%:1.428–2.666), previous decompensation (HR: 1.360;CI95%:1.041–1.777), platelet count (HR:1.002; CI95%:1.000–1.005) and AST>UNL (HR:1.612;CI95%:1.261–2.061) were independently associated with higher risk of ACM. Conversely, abstinence (HR:0.642;CI95%:0.505–0.815) was associated with lower risk. LRM at 5, 10 and 20 years was 17%, 30% and 52%. Variables associated with higher risk of LRM were: age (HR 1.032;CI95%:1.013–1.050), male sex (HR:2.052;CI95%:1.340–3.142), previous decompensation (HR:1.883;CI95%:1.338–2.651), Child B (HR:1.681; CI95%:1.242–2,330), platelet count (HR:1.005;CI95%:1.002–1.008) and AST>ULN (HR:1.701;CI95%:1.242–2.330). Abstinence (OR:0.553; CI95%:0.414–0.738) was associated with a lower risk. Non LRM at 5, 10 and 20 years was 8%, 18% and 48%. Variables associated with higher risk of non LRM were age (HR:1.038;CI95%:1.011–1.066), BMI<25 (HR:2.581;CI95%:1.579–4.218), tobacco use (HR:1.844;CI95%:1.111–3.060) and inclusion after 2005 (HR:2.184;CI95%:1.332–3.581), while abstinence was associated with risk reduction (HR:0.616; CI95%:0.421–0.902).
Conclusion: Alcohol abstinence in patients with alcohol-related cirrhosis reduces the risk of any cause mortality, liver-related mortality as well as non liver-related mortality. However, variables associated with advanced liver disease have a substantial weight on liver-related and all cause mortality; consequently, early diagnosis of alcohol-related liver disease is essential.

THU066
Non-invasive criteria for diagnosis of alcoholic hepatitis: use in clinical practice and correlation with prognosis

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Background and Aims: liver biopsy is still considered the gold standard for the diagnosis of alcoholic hepatitis (AH). Nonetheless, in clinical practice diagnosis of AH is frequently done by clinical and analytical criteria. International guidelines recommend the use of clinical criteria for diagnosis of alcoholic hepatitis in clinical practice. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) clinical criteria were recently proposed for clinical diagnosis of AH. However, to date, studies on the correlation between NIAAA criteria and histological criteria for the diagnosis of AH are still lacking. The aim of this study was to evaluate the consistency among NIAA clinical criteria and the histological criteria for diagnosis of AH.
Method: a prospective cohort of patients with alcohol related liver disease who underwent a liver biopsy was studied in a 4-year period. In this cohort, two groups were characterized retrospectively based on the pre-biopsy probability of presenting AH in high or low probability of AH. Pre-biopsy high probability of AH was defined in those patients with jaundice accompanied or not by clinical decompensation of cirrhosis and active alcohol consumption, in which the reason for liver biopsy was referred as "suspicion of AH" in the medical records. Patient's clinical and laboratory information was collected prospectively at baseline and during the follow-up. Histological characteristics and NIAAA clinical criteria (jaundice in the previous 8 weeks, alcohol intake of more than 40/60 g in female/male, AST >50 UI/l, ratio AST/ALT >1.5 and both <400 UI/l, bilirubin>3 mg/dl) were reviewed retrospectively in all the patients.
Results: 114 patients were included; among them 63 (55%) had high pre-biopsy probability of AH and 51(45%) low. Histological criteria for AH were met by 59 patients and NIAAA criteria by 48. Positive predictive value (PPV) of NIAAA criteria for AH diagnosis was 81% (34 out of 48) with a false negative rate(FNR) of 30% (20 out of 66). In the high HA pre-biopsy probability group, NIAAA PPV was 84% (33 out of 39) with a FNR of 53% (7 out of 13). One-year overall survival rate was 77% in the whole cohort. Patients who met both NIAAA and histological criteria of AH had the worst survival rate (62%), followed by those that only met histological criteria for AH (75%); instead, patients who were diagnosed with AH only through NIAAA criteria but did not meet histological criteria had similar survival rate to that of patients without AH (87% in both cases, p = 0.039).
Conclusion: in a not-selected cohort of patients with alcoholic liver disease diagnostic power of the NIAAA clinical criteria was moderate, with a not negligible amount of false positive and false negative rates. This fact is clinically relevant considering that patients with histologically proven AH have a worse prognosis.

THU067
Early life ethanol exposure has long-term impacts on the transcriptome and epitranscriptome of rat liver

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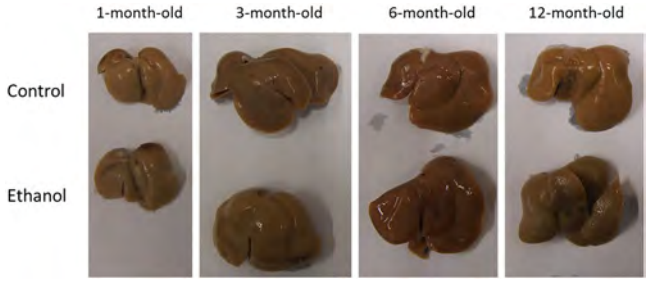
Background and Aims: Fetal alcohol spectrum disorder (FASD) is a birth defect due to maternal alcohol consumption during pregnancy. Children with FASD are characterized with neurobehavioral deficits and growth anomalies, but little is known about liver histopathologic and molecular features in patients with FASD. Thus we aimed to investigate whether early life ethanol exposure could have long-term impacts on liver development and genomic constitution.
Methods: In a rodent model of FASD, rat pups were given ethanol (5.25 g/kg/day) via oral intubation on postnatal day (PD) 4–9 (equivalent to human third trimester), then the livers from ethanol-treated and age-matched control littermates were collected at different ages (1, 3, 6, and 12 months of life) for high-throughput RNA sequencing, reverse transcription PCR (RT-PCR) and histological analysis.
Results: Consistent with case reports from human FASD patients, livers from our animal model exhibited hepatomegaly and fat deposition in hepatocytes, and these histopathologic features lasted up to 12 months of life. Both transcriptome and epitranscriptome were also persistently and concordantly changed, with genes involved in the lipid metabolism and immune system were most affected.



Conclusion: Early life ethanol exposure can cause long-lasting deleterious alterations in liver at both histological and molecular levels. The identified molecular signatures not only contribute to the

etiology of early life ethanol-induced liver pathogenesis, but also provide as potential targets for therapeutic intervention.

THU068

Alcohol recurrence and outcome in patients transplanted for alcoholic cirrhosis: impact of the 6-month rule

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Background: Liver transplantation (LTx) is generally recommended for patients with decompensated alcoholic cirrhosis (Meld>15) with a time from alcohol abstinence to LTx >6 months. The latter rule is still debated as the 6-month per says could not contraindicate alone LTx in the last guidelines. On the other hand, early LTx became a possible option for treatment of highly selected patients with acute alcoholic hepatitis (AAH) non-responding to medical treatment.
Method: This is a retrospective study that recruited in our center all LTx patients for alcoholic cirrhosis during the period of 2013–2017. Patients were stratified into 3 groups according to period of abstinence prior to LTx: >6 months (group 1); <6 months (group 2) and biopsy proven AAH refractory to medical treatment (group 3). Alcoholic recurrence was defined by any alcohol consumption reported by the clinicians, or on oriented/protocol liver biopsies and prospectively by a specific survey send to all patients. The survey allowed characterizing the recurrence via the AUDIT-C score.
Results: Among the 172 LTx patients recruited in the study, 21 and 13 patients were respectively in group 2 and 3. The mean MELD score at time of LTx was respectively 19.4 ± 9.3, 31.6 ± 10.7 and 34.6 ± 8.4 (Group 1, 2 and 3). The 1 and 5-year patient survival were respectively 93%, 84% and 100% and 79%, 76% and 100% (Group 1, 2 and 3, global Log rank, p = 0.24). Overall, 46 patients had post-transplant alcohol recurrence. Of the 122 patients who responded to the survey, 16 patients with a recurrence not identified by the clinicians were revealed. Alcohol recurrence rates were respectively 26%, 24% and 54% in groups 1, 2 and 3 (p = 0.5). In the multivariate analysis, factors associated with alcohol recurrence were AAH {OR = 5, 95%CI (1.49–17.43), p = 0.009}, consumption of toxic substances prior to LTx {OR = 3.24, IC95% (1.13–9.25), p = 0.028}. The fact that in the survey the patient admit that alcohol was the leading cause of his cirrhosis was a protective factor for recurrence {OR = 0.39, 95%CI (0.11–1.29), p = 0.12}.
Conclusion: AHH and consumption/abuse of toxic substances prior to LTx were the main determinant of post-transplant alcohol recurrence. The absence of differences in survival and recurrence rate between group 1 and 2 support the fragility of the 6-month rule and the importance of a multidisciplinary and a multifactorial approach for optimal selection of these patients to LTx.

THU069

Early liver transplantation in active drinkers with and without alcoholic hepatitis: a monocentric case series

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Background and Aims: Early liver transplant (eLT) is an effective therapeutic option for patients with severe alcoholic hepatitis (SAH). Whether eLT should also be offered to active drinkers with rapidly progressive acute liver failure who do not have a definite diagnosis of SAH, is unknown. Here we report the outcome of eleven active drinkers with severe acute liver impairment and diagnosis of probable SAH who received eLT.
Method: all active drinkers consecutively admitted to our unit from April 2016 to June 2019 with clinically diagnosed "probable SAH" defined according to NIAAA criteria and with a Maddrey Score (MS) >32, were included in the study. Patients not improving after medical therapy, irrespective of the use of steroids, were evaluated for eLT. The definite diagnosis of SAH was based on the histology of the explanted liver. Psycho-social selection performed by a dedicated team and tailored support pre- and post-LT were the cornerstone of the program.

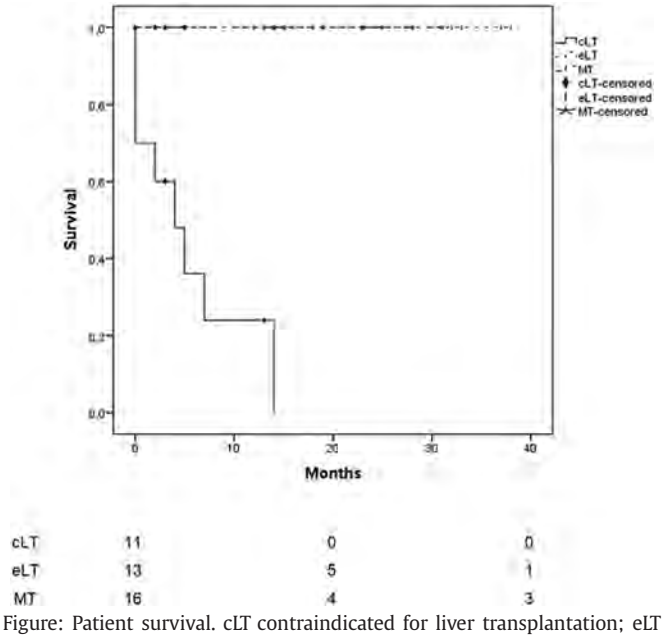

Figure: Patient survival. cLT contraindicated for liver transplantation; eLT early liver transplantation; MT improved with medical treatment/support (two patients received liver transplant beyond six months).

Results: Forty consecutive patients with alcoholic cirrhosis and acute severe liver failure due to probable SAH were enrolled. The great majority (33/40, 82%) did not receive CS mainly for active infection (24/40, 60%). Sixteen (40%) patients, with median baseline MS 64 and MELD-Na 24, improved with medical treatment/support (MT). None died after a median follow up of 14 months (5–23); two received liver transplant beyond six months. The remaining twenty-four patients were evaluated for eLT. Eleven (27.5%) patients were excluded from eLT due to psychiatric or medical contraindication. Median FU in this group was 4 months (0–7). Thirteen (32.5%) patients, with a median baseline MD 94 and MELD-NA 36, underwent eLT. All patients undergoing eLT are alive, after a median follow up of 18 months (12–33) To date one patients relapsed in heavy alcohol use about 25 months after eLT. On explant, all LT recipients had cirrhosis with only 6 also having alcoholic steato-hepatitis confirmed.
Conclusion: eLT should be considered in active drinkers with acute severe liver failure irrespective of definite diagnosis of SAH. Stringent psycho-logical support pre and post LT is crucial to avoid alcohol relapse.

THU070

Long-term outcome of symptomatic alcoholic hepatitis with a Maddrey discriminant function <32

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Background and Aims: Patients with alcoholic hepatitis and a modified Maddrey's discriminant function (mDF) <32 have a low risk of short-term mortality. However, few data exist concerning long-term outcomes. The aims of this study were to evaluate 5-year survival rates and to identify predictive factors for long-term prognosis in this patient population.

Method: We studied patients from 2 centres who were admitted for hepatic decompensation (ascites, hepatic encephalopathy, or jaundice) and who had histological findings of steatohepatitis and an mDF <32. Clinical and biological parameters were recorded at the time of liver biopsy and alcohol consumption was recorded during follow-up. We performed Cox proportional hazard survival analysis to identify factors associated with 5-year survival.

Results: One hundred and twenty-one patients were included (male: 64%, mean age: 51.5 ± 10.3 years, presence of cirrhosis: 84%). The median MELD and mDF scores were 14 [25th–75th percentile: 11.7–16.1] and 19 [25th–75th percentile: 11.1–24], respectively. During follow-up, 30% of the patients remained abstinent. Survival rates at 1, 6, 12, 24, and 60 months were 96.7 ± 1.6%, 90.1 ± 2.7%, 80.8 ± 3.6%, 69.9 ± 4.3%, and 50.7 ± 4.9%, respectively. The majority of deaths (80%) were liver-related. In multivariable analysis, encephalopathy at baseline and alcohol abstinence were predictive of 5-year survival. The 5-year survival rates of patients without and with encephalopathy at baseline were 60.5 ± 5.8% and 29.7 ± 8%, respectively, and the 5-year survival rates of abstinent and non-abstinent patients were 74.8 ± 8% and 40.9 ± .8%, respectively.

Conclusion: Mortality of patients with alcoholic hepatitis and an mDF <32 presenting with an acute decompensation is around 50% at 5 years. Hepatic encephalopathy at baseline and lack of alcohol abstinence impair long-term prognosis. New treatment strategies, including measures to ensure abstinence, are required.

THU071

Genetic variant PNPLA3 I148M accelerates fat accumulation in livers of mice with ASH/NASH via damping of PPAR alpha and PPAR gamma signalling pathways

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Background and Aims: Non-alcoholic (NAFLD) and alcoholic (ALD) liver disease are leading causes of progressive fatty liver disease, particularly in patients with both entities. *PNPLA3* rs738409 is a risk locus for progressive NAFLD, NASH and ALD, but the exact mechanism of how the loss of function in the PNPLA3 gene drives progression is incompletely understood.

Method: Variant *PNPLA3* rs738409 (*PNPLA3*^{I148M}) mutation was introduced to C57Bl6 mice by CRISP-Cas9-based genome editing and confirmed by sequencing. Hepatic steatosis was induced by a combination of alcohol (10% in drinking water) and Western Diet (WD, TD.88137) (EtOH/WD) for 25 weeks. Liver fibrosis, inflammation, steatosis and damage were assessed by blood and tissues histology, qPCR and various biochemical analyses and compared between groups.

Results: EtOH/WD resulted in body, liver and spleen weights increases, but no modulating effect of genotypes was found. In line, hepatic fibrosis levels, measured by hydroxyproline, ALT, AST, as well as *PC alpha 1(I)*, *TGF beta 1*, *alpha SMA* mRNAs, did not differ between *PNPLA3*^{WT} and *PNPLA3*^{I148M}, whereas inflammation markers *IL1 beta, Cxcl1, Cxcl2 and IL-10* mRNA were highly upregulated (up to 2-fold, $p < 0.05$) in *PNPLA3*^{I148M}. In addition, *PNPLA3*^{I148M} showed 16% higher hepatic TG content compared to *PNPLA3*^{WT} ($p = 0.01448$), while in cirrhotic *PNPLA3*^{I148M} it was non-significantly reduced. *PPAR alpha* and *PPAR gamma* were 30–50% downregulated in both – fibrotic and cirrhotic *PNPLA3*^{I148M} on EtOH/WD, as well as the expression of *Scd1, FADP4, FASN* and *Cidec* were suppressed. Interestingly, in *PNPLA3*^{I148M} on a control diet, *FASN* and *IL1 beta* were 1.6- and 4-fold induced, respectively, if compare to *PNPLA3*^{WT}.

Conclusion: Presence of *PNPLA3* rs738409 results in enhanced fatty acid synthesis, decreased activity of *PPAR alpha* and *PPAR gamma* and consequent suppression of beta-oxidation, eventually leading to enhanced triglyceride formation in response to an EtOH/WD treatment as a model of *hedonism-associated steatohepatitis* (HASH).

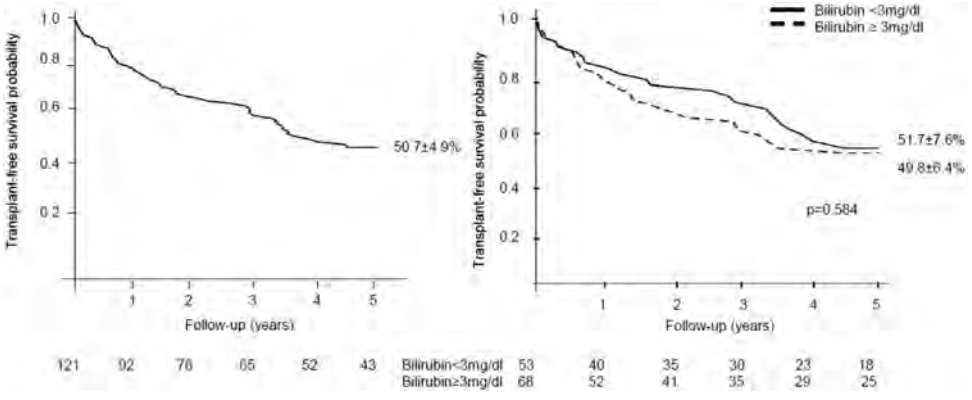

Figure: (abstract: THU070)

THU072

Delisting of liver transplant candidates after improvement in alcohol-related decompensated cirrhosis: a multicentric study on incidence and outcomes

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Background and Aims: Delisting following recompensation has been reported in a proportion of liver transplant (LT) candidates, particularly HCV-infected patients when viral eradication is achieved. The information regarding this issue is much scarcer for other etiologies of liver disease. We aimed to investigate delisting for improvement in a multicentric cohort of LT candidates, focusing on patients with alcohol (ETOH)-related cirrhosis.
Method: Retrospective study within the OCATT registry data. All LT candidates admitted in the waiting list (WL) for LT due to decompensated cirrhosis (DC) in Catalonia (Spain) between 2007 and 2018 were included. The etiologies of liver disease considered were ETOH, HCV, non-alcoholic fatty liver disease (NAFLD), cholestatic, and others. Patients with mixed etiologies and those admitted in the WL for indications other than DC were excluded. We analyzed the probability of delisting due to improvement in the whole cohort and according to the etiology. In ETOH DC patients, baseline characteristics associated with delisting for improvement were evaluated, and clinical outcomes of these patients described.
Results: During the study period, 1230 patients with DC were admitted in the WL (420 ETOH, 403 HCV, 70 NAFLD, 108 cholestatic, 229 others). In the whole cohort, 6.2% of patients were delisted for improvement. In patients with ETOH DC, probability of delisting was 8.6% (n = 36), similar to that in HCV (7.7%, n = 31), and significantly higher than in patients with NAFLD (1.4%, n = 1), cholestatic diseases (1.8%, n = 2), or other causes (3.1%, n = 7) (p = 0.04). In patients with ETOH DC, delisting for improvement was more likely in women (18% vs 7%, p = 0.025), and in patients with lower MELD score at WL admission (p < 0.001). After a median follow-up of 44 months after delisting, 67% of ETOH DC delisted (n = 24) remained alive without LT, 6% (n = 2) were readmitted in the WL and underwent LT, 11% (n = 4) died due to non-hepatic causes, and 17% (n = 6) died due to liver-related causes.
Conclusion: Delisting following improvement is relatively frequent in ETOH and HCV DC, and extremely rare in other etiologies of liver disease. Female gender and low MELD score at WL admission are associated with higher chances of delisting for improvement in ETOH DC. After delisting for improvement in ETOH DC, the incidence of liver complications is similar to that reported in the literature in patients with HCV that are delisted after viral eradication.

THU073

A novel lymphocyte proliferation assay accurately predicts 90-day survival in severe alcoholic hepatitis patients

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Background and Aims: Severe alcoholic hepatitis (SAH) is an inflammatory condition with high mortality (37.8% at 6 months)[1]. Corticosteroids are the only current therapy to improve short term outcome but one third fail to respond. Identifying patients whom corticosteroid treatment would benefit is crucial. The Dexamethasone Inhibition of Lymphocyte Proliferation Assay (DILPA), accurately predicts 6-month survival in SAH patients[2]. An improved radiation-free assay, bromodeoxyuridine (BrdU) incorporation in lymphocyte steroid sensitivity (BLISS) assay, has been developed and validated in healthy controls[3]. We assessed the diagnostic capability of BLISS in SAH patients.
Method: Peripheral blood was drawn from patients between 0–72 hours of presenting to University Hospitals Plymouth NHS Trust with a clinical diagnosis of SAH (heavy alcohol use, new jaundice, coagulopathy, discriminant function [DF] >32). The primary outcome measure was 90-day survival. Peripheral blood mononuclear cells, isolated by density gradient centrifugation, were stimulated with lymphocyte mitogen in the absence or presence of dexamethasone and cultured for 48 hours as previously described[3]. Proliferation was determined by measuring BrdU incorporation using a commercial kit. The maximum suppression of proliferation by corticosteroids (Imax) was calculated.

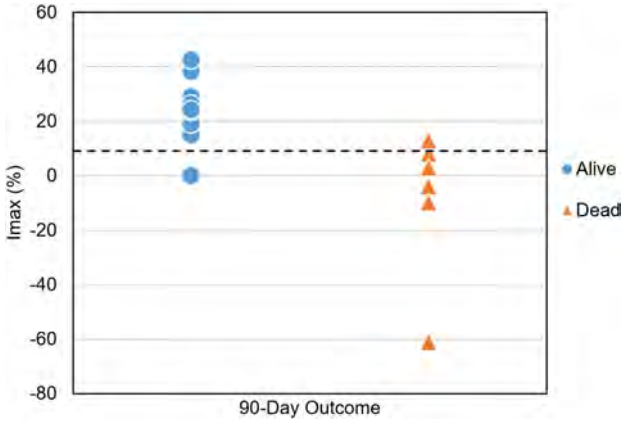

Figure 1. Imax values of SAH patients grouped by 90-day outcome.

Results: 16 patients were recruited (8 female, median age 50, mean DF 67.1) 10 patients survived to 90 days, having significantly higher Imax than non-survivors (23.80% v –0.5%; p = 0.002) with a single data point overlapping between groups (Figure 1). AUROC for Imax was 0.95 (95% CI 0.84–1.0). Using the optimum cut-point of Imax 14% had a sensitivity of 90% in identifying steroid responsive patients with a negative predictive value of 86%. Lille score of survivors was lower than non-survivors (0.32 v 0.84; p = 0.005), however applying the established threshold of 0.45 misclassified 2 patients as steroid non-responders. Imax did not correlate with Lille score (r^2 = 0.06).
Conclusion: The BLISS assay differentiates survivors from non-survivors at 90 days, showing promise as a tool to determine the patients most suited to corticosteroid treatment. Validation in a larger multicentre cohort is underway as part of the Multicentre Cohort Study in AH (MICAH) trial.

References

1. Louvet et al., 2018. *Gastroenterology*
2. Dhanda et al., 2015. *Hepatology*
3. Williams et al., 2016. *Biomarker research*

THU074

Alcohol use disorder and liver fibrosis - cases are missed through failure to test

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Background and Aims: Alcohol Use Disorders (AUD) account for 7.2% hospital admissions per year in the UK. While a proportion of these people are recognised to have liver disease and are managed by liver specialists, many are managed by a wide range of physicians and their liver disease may be missed even if their AUD is recognised. We aimed to use non-invasive tests for liver fibrosis to investigate the prevalence of occult liver disease in patients recognised to have AUD but not known to have liver disease.
Method: Prospective service evaluation of liver fibrosis in consecutive patients referred to the Alcohol Specialist Nurse (ASN) at the Royal Free Hospital from Nov' 2018–19. Patients were excluded if they were already known to have liver disease. Liver fibrosis was assessed using the Enhanced Liver Fibrosis (ELF) test performed on serum extracted from 5 ml of blood, analysed on an Advia Centuar. Patient demographic, blood test and imaging data were recorded along with alcohol histories. Patients with ELF scores ≥ 10.5 were invited for fibroscans and outpatient hepatology assessments.
Results: We included 85 patients (71.8% male), mean age of 52 (±13.8). Median alcohol intake was 140 units/week (IQR 87–280) and mean duration of excess alcohol 18 years (±13.4). The commonest reason for presentation to hospital was symptomatic alcohol withdrawal (n = 33/85). Other reasons included falls/trauma (10/85), pancreatitis (8/85), mental health (10/85), and 'other' (24/85). None had a prior history of liver disease. Three patients had documented signs of CLD. Liver function tests, checked in 81/85 patients were abnormal in 56/81 (69.1%). ELF scores ranged from 6.87–13.78, (mean = 9.82 ± 1.23). Of the total cohort, 22/85 (26%) had an ELF score ≥ 10.5. Of these, 25% had normal LFTs. All but one (84/85) had previously attended A&E in the last 5 years, (median number of presentations = 4, IQR 1.5–9) without assessment or diagnosis of liver disease.
Conclusion: Over a quarter of patients in this cohort with AUD had evidence of advanced liver fibrosis that had been undetected prior to 'opportunistic' ELF testing. The vast majority had had recent hospital attendances representing additional missed opportunities for investigating liver disease. LFTs cannot be relied upon to for detection of liver disease in AUD. We propose that clinicians consider using non-invasive tests to assess liver fibrosis in all patients admitted to hospital with AUD.

THU075

Decreasing incidence of alcoholic liver disease in Denmark: a nationwide study

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Background and Aims: Alcohol exposure has decreased in Denmark since 1994. We described the incidence, prevalence, and hospital care of alcoholic liver disease during the last two decades.
Method: Through the nationwide healthcare registries, we identified all Danish patients with a first-time diagnosis of alcoholic liver disease (ICD-10: K70.x) in the 1994–2017 period. We computed standardised incidence rates, standardised prevalence, and we enumerated inpatient admissions and outpatient and emergency room visits. Moreover, we computed incidence rates by 5-year birth cohorts (1930–1979) and 5-year age groups (30–79 years).
Results: The standardised incidence rate of alcoholic liver disease peaked at 362 (95% CI: 346–378) per 1,000,000 population in 2009 and decreased steadily to 258 (95% CI: 245–271) per 1,000,000 population in 2017. This decrease was most pronounced in men aged 15–44 and women aged 45–64. The 1950–1959 birth cohorts had the highest age-specific incidence rates, and the rates decreased sequentially with each following birth cohort. The number of inpatient admissions and emergency room visits decreased from 2009 to 2017, while the number of outpatient visits increased. The prevalence of alcoholic liver disease (0.22%) and the mean admission length per inpatient admission (6.5 days) were stable from 2009 onwards.

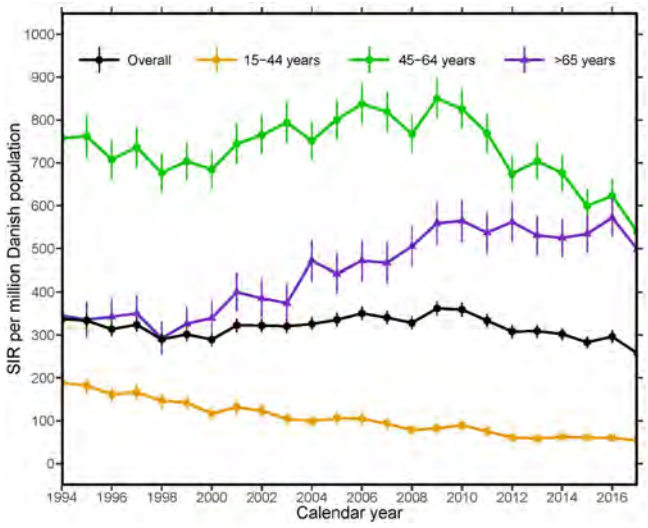

Figure: Standardised incidence rate (SIR) of alcoholic liver disease per million Danish population by age groups 1994–2017.

Conclusion: The incidence and overall hospital burden, but not the prevalence, of alcoholic liver disease has decreased since 2009 in Denmark. We anticipate a further decrease in the incidence of alcoholic liver disease in the future, since younger birth cohorts with a lower age-specific incidence have yet to reach the age of peak alcoholic liver disease incidence.

THU076

Fibroblast growth factor 21 response in a preclinical model of alcohol induced acute-on-chronic liver injury

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Background and Aims: Fibroblast growth factor (FGF) 21, the major regulator of glucose and lipid homeostasis, has been shown to play a potential role in bile acid metabolism. Here we aim to investigate FGF21 response in an ethanol-induced acute-on-chronic liver injury (ACLI) model in *Abcb4*$^{-/-}$ mice with deficiency of the hepatobiliary phospholipid transporter.
Method: Total hepatic and ileal RNA was extracted from wild-type (WT) C57BL/6J and *Abcb4*$^{-/-}$ (KO) mice, which were either fed control diet (WT/Cont and KO/Cont groups) or ethanol diet (5% v/v), followed by an acute ethanol binge (5 mg/kg) (WT/EtOH and KO/EtOH groups; n = 28/group). Hepatic expressions of *Fgf21*, *Fgfr1*, *Fgfr4*, *Klb*, *Srebf1*, *Cyp7a1*, *Cyp8b1*, *Cyp27a1*, *Shp*, *Fxr*, *Ppara* and *Mtor* as well as ileal mRNA levels of *Fgf15*, *Fgfr1*, *Klb*, *Fxr* and *Diet1* were evaluated using the $2^{-\Delta\Delta Ct}$ method. Plasma FGF15 and FGF21 levels were determined by ELISA.
Results: Ethanol exposure significantly upregulated *Fgf21* in WT and *Abcb4*$^{-/-}$ mice ($p = 0.009$ and 0.026, respectively) as compared to their control diet-fed counterparts, although no significant difference was observed. FGF21 elevation was demonstrated in plasma of WT/EtOH and KO/EtOH groups ($p = 0.040$ and 0.048, respectively). No

differences were observed for hepatic expression of *Fgfr1*, *Fgfr4*, *Klb*, *Srebf1*, *Shp*, *Fxr* and *Mtor* between groups. Ethanol challenge resulted in significant induction of hepatic *Ppara* expression in both WT (p = 0.021) and KO mice (p = 0.023). Of note, *Cyp7a1* and *Cyp27a1* were significantly repressed in livers from WT/EtOH (p = 0.044 and p = 0.007, respectively) and KO/EtOH groups (p = 0.035 and p = 0.001, respectively), as compared to WT/Cont. Significant repression of *Cyp8b1* was observed only in KO/EtOH group in comparison to WT/Cont (p = 0.041), WT/EtOH (p = 0.029), and KO/Cont groups (p = 0.027). While plasma FGF15 levels did not differ between groups, ileal expression of *Fgf15* and *Fxr* was induced in WT/EtOH compared with WT/Cont mice (p = 0.029 and p = 0.007, respectively). Ileal *Fgfr1, Klb* and *Diet1* did not differ.

Conclusion: Hepatic expression of *Cyp7a1,* which encodes the rate-limiting enzyme of bile acid synthesis, was markedly suppressed after alcohol consumption, regardless of genotype. Simultaneous upregulation of *Fgf21* and repression of *Cyp7a1* in liver, concurrently with invariant hepatic *Shp, Fxr, Klb* and *Fgfr4* and plasma FGF15 levels, suggest that upon ethanol challenge, bile acid metabolism might be regulated by FGF21, resulting in inhibition of *Cyp7a1* through an FGF15-independent pathway in our model.

THU077

Mortality in biopsy-proven alcohol-related liver disease: population-based cohort study of 3,453 individuals

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Background and Aims: Patients with alcohol-related liver disease (ALD) are at increased risk of death, but current risk estimates rarely accounts for histological disease severity and lacks a matched reference population for comparison. We examined overall and disease-specific mortality in a nationwide cohort of biopsy-proven ALD.

Method: Population-based cohort study in Sweden. Individuals with an ICD code for ALD and a liver biopsy between 1969–2017 were included and compared to an age-, gender-, year- and municipality-matched reference population. Histopathology subgroups of ALD patients were studied. National registers were used to ascertain overall and disease-specific mortality. Cox regression adjusted for relevant confounders was used to estimate hazard ratios (HRs).

Results: We identified 3,453 patients with ALD that were matched to 16,535 reference individuals. Median age at baseline was 58 years, 65% were men and 52% had cirrhosis. After a median follow-up of 5.7 years (range 0.3–47.1), 74% (deaths = 2,557) of all patients with ALD died, compared to 31% (deaths = 5,107) of controls (adjusted [aHR] = 4.70; 95%CI = 4.35–5.08). The risk of liver-related death was particularly high (43% of all deaths, aHR = 167.6, 95%CI = 101.7–276.3). Mortality was significantly increased also in ALD patients without cirrhosis, was highest in the 12 month period after biopsy, but persisted after ≥ 10 years of follow-up (aHR = 2.74; 95%CI = 2.37–3.16). Heavy drinking was found in around 1/3 of ALD patients after baseline and was associated with a higher risk of mortality (aHR 1.30, 95%CI = 1.21–1.41).

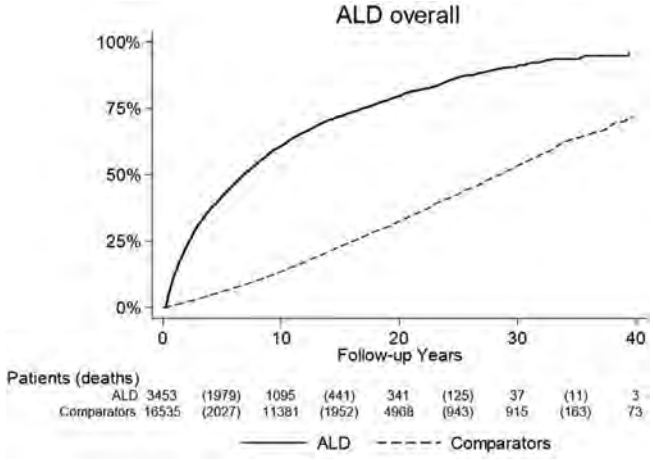

Figure: Kaplan-Meier failure curve of overall mortality or liver transplantation in patients with ALD, compared to reference individuals.

Conclusion: Persons with biopsy-proven ALD has an almost five-fold risk of dying than the general population. Risk estimates can be used to better inform clinicians and patients on short-term and long-term risks in ALD.

THU078

Inhibition of cytochrome P-4502E1 by clomethiazole improves alcoholic liver disease in alcohol-dependent patients: a short-term, randomized, controlled clinical trial

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Background and Aims: Alcoholic liver disease (ALD) is a major health problem worldwide without effective treatment options except abstinence thus far. The pathophysiology of ALD includes, among others, oxidative stress via generation of reactive oxygen species (ROS). ROS cause lipid-peroxidation, protein alterations, and DNA injury. One important source of ROS is microsomal ethanol metabolism catalyzed by cytochrome P4502E1 (CYP2E1). Chronic ethanol consumption induces CYP2E1 primarily in the liver and, thus, deteriorates ALD and stimulates alcohol-mediated carcinogenesis in animals. Conversely, inhibition of CYP2E1 by clomethiazole (CMZ), a strong CYP2E1 inhibitor, decreases oxidative stress in cell cultures and improves ALD in animal studies.

Method: To study whether CYP2E1 inhibition improves ALD in humans, we performed a randomized controlled clinical trial in alcohol-dependent patients who were admitted for alcohol detoxification therapy (ADT) (EudraCT 2012-005730-11). All patients were non cirrhotic as identified by fibroscan <12 kPa and all had serum AST activity of more than twice the upper limit of normal. The patients were randomly assigned for ADT either with CMZ (n = 27) or clorazepate (CZP; n = 27) for 7 to 10 d.

Results: CMZ almost completely inhibited CYP2E1 measured by chlorzoxazone test 24 h after start of CMZ (p < 0.0001). Already after 4 d of treatment, serum AST- (mean ± SEM: 97 ± 11 vs. 59 ± 7 U/l; p < 0.04) and ALT activity (110 ± 14 vs. 70 ± 10 U/L; p < 0.02) were significantly lower during CMZ than during CZP. After 8 d of treatment serum transaminase activity between the two groups was as follows (AST: 73 ± 11 vs. 47 ± 5 U/l; p < 0.004 and ALT: 108 ± 14 vs. 55 ± 8 U/l; p < 0.0006). Concurrently, ADT with CMZ significantly decreased hepatic fat content (p < 0.05) as evaluated by controlled attenuation parameter (CAP), but not during CZP (p = 0.081). Similarly, only with CMZ a significant correlation was found

between hepatic fat at admission and the change of hepatic fat between admission and discharge ($r = 0.64$; $p < 0.001$).
Conclusion: This study underlines for the first time in humans the role of CYP2E1 as a pathogenic factor in ALD and shows that its inhibition improves ALD. Because CMZ with its addictive potential can only be given for a short period of time, it is mandatory to search for non-toxic CYP2E1 inhibitors to treat ALD.

THU080

Role of fecal microbiota transplantation in severe alcoholic hepatitis: assessment of impact on prognosis and short-term outcomes

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Background and Aims: Severe alcoholic hepatitis (SAH) transitioning to acute on chronic liver failure, mortality rate often exceeds 50%. Targeting intestinal dysbiosis, found to be intricately linked with the disease's pathogenesis, could provide insights into novel therapeutic strategies. This study was conducted to evaluate the role of fecal microbiota transplantation (FMT) on short-term survival, prognostic scores and to assess its feasibility, tolerability and safety.
Method: Patients aged 18–60 years with SAH were included. Patients received a 5-day oral antibiotic course prior to the FMT procedure. Healthy consenting family members were selected as stool donors after screening. FMT was performed in a single setting with freshly prepared (6 hours) stool suspension constituted from 30 g of donor stool homogenized with 100 mL of normal saline delivered through a nasojejunal tube. The patients were followed up on days 7, 30 and 90 post procedure. Matched controls received standard of care (SOC) during the same period.
Results: 51 patients with SAH were screened; 33 satisfied the inclusion criteria, of which 13 (39.4%) consented to FMT. Mean age (39.6 vs 40.7 years), Child-Pugh (11.5 vs 12.1), Model for End-stage Liver Disease (25.2 vs 25.6) and Maddrey's discriminant function (87.0 vs 83.6) scores at baseline in FMT vs SOC arms were not significantly different. 1- and 3-month survival rates were higher in patients in FMT arm compared to those in SOC arm (Table). Resolution of hepatic encephalopathy and ascites were higher in patients in FMT arm compared to those in SOC arm (Table). Event rates of spontaneous bacterial peritonitis and upper gastrointestinal bleed were similar in both groups (Table). Excessive flatulence (100%), gastroesophageal reflux (53.8%) and nausea (23.1%) were the commonest side effects in patients in the FMT arm.

Parameter	FMT arm	SOC arm	P value
N	13	20	
Mean age (Years)	39.6 ± 17.1	40.7 ± 13.1	0.68
1-month survival	13 (100%)	12 (60%)	0.016
3-month survival	7 (53.8%)	5 (25%)	0.14
Resolution of hepatic encephalopathy	6/6 (100%)	8/14 (57.1%)	0.11
Resolution of ascites in survivors	7/7 (100%)	2/5 (40%)	0.045
Spontaneous bacterial peritonitis	4/13 (30.76%)	5/20 (25%)	1.0
Upper gastrointestinal bleed	3/13 (23.07%)	7/20 (35%)	0.70

Conclusion: FMT was feasible, tolerable and safe in patients with SAH. FMT was associated with a lower one-month mortality rate and higher rate of ascites resolution. There was a trend toward improved three-month survival and resolution of hepatic encephalopathy.

THU081

In alcoholic hepatitis, cytokeratin 18 serum fragments reflect its severity and predict responsiveness to prednisolone

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Background and Aims: Up to 40% of patients with severe alcoholic hepatitis (sAH) die within 6 months of presentation making prompt diagnosis and appropriate treatment essential. Cytokeratin 18 (CK18) serum fragments have been widely used as markers of hepatocellular injury. The aim was to determine the association between serum CK18 and histological features, prognosis, and a differential response to prednisolone in patients with sAH.
Method: CK18-M65 and CK18-M30 were quantified in pre-treatment serum from patients recruited to the Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) trial ($n = 824$). Histology was assessed using the Laennec fibrosis grade and Alcoholic Hepatitis Histological Score in 134 available cases.
Results: CK18-M30 and CK18-M65 levels were higher in cases with severe inflammation (both $p < 0.0001$) or ballooning (both $p < 0.01$) on biopsy. Serum CK18-M30 ($p = 0.0016$) and CK18-M65 ($p = 0.0032$) were both significantly associated with 90-day mortality in patients who did not receive prednisolone. A significant interaction was noted between prednisolone and high serum CK18-M30 (defined as >5000 IU/L, $p_{interaction} = 0.0162$). When dichotomised by this cut point, prednisolone was associated with a significant reduction in mortality in those with high (odds ratio 0.43, 95% confidence interval 0.19–0.95, $p = 0.040$) but not low, CK18-M30 (odds ratio 1.27, 95% confidence interval 0.88–1.84, $p = 0.20$).
Conclusion: In patients with sAH serum CK18 fragments are strongly correlated with its severity and 90-day mortality. A cut-off of CK18-M30 >5000 IU/L appears to define a population of patients with severe inflammation in whom a beneficial response to prednisolone is seen at 90 days.

THU082

Multi-modal training of specialty clinical trainees improves the detection and subsequent interventions for alcohol use disorder

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Background and Aims: Pts seen in hepatology clinics require alcohol use disorder (AUD) screening. While usually done directly, a structured approach using AUDIT-10 is preferred. We first collected data retrospectively regarding AUD detection, aimed to train providers and follow them prospectively to gauge improvement.
Method: *Retrospective(Retro)*: Clinic encounters over the last 1 yr were evaluated by 2 reviewers in 2 cohorts (Cohort 1: 6mth-1 yr prior to training & cohort 2: 6 mths-end). Encounters were evaluated for (1) whether alcohol was asked about (2) if yes, was it followed by AUDIT-10 & (3) was intervention suggested. *Training*: GI providers were asked about AUD & training was provided to ask pts regarding alcohol & follow up with AUDIT-10 & referral as neeeded. AUDIT-10 templates in the EMR were shown. *Prospective(Prosp)*: Similar data as the retro study were collected for 6 mths post-training. Changes in (a)

alcohol inquire (b) AUDIT-10 provision (c) alcohol-related counselling & interventions between cohorts were compared.
Results: *Training*: 17 providers (10 trainees) underwent training. Most trainees had little familiarity with DSM-V criteria, were unfamiliar with AUDIT-10 & did not consult with mental health. *Pt comparisons*: 239 pts were in retrospective cohort 1 (95% men), 139 in cohort 2 (96% men) and 125 (95% men) were in the prospective group. Groups were similar with respect to age, advanced fibrosis, alcohol etiology, & active alcohol use. *Alcohol-related activities*: Significantly higher percent in the prosp received counselling. In pts with active drinking, further inquiry via AUDIT-10 was higher in prosp pts. This resulted in higher intervention rates compared to both retro gps. Missed opportunities were lower in prosp pts. No differences were seen between the 2 retro cohorts.

Table: Comparison between retrospective and prospective cohorts

N (%) or mean ± SD	Retro 1 (n = 239)	Retro 2 (n = 139)	Prosp (n = 125)	P value (all gps)
Age	62.8 ± 9.4	61.5 ± 9.0	62.3 ± 9.4	0.61
F0-F2/F3-F4 Fibrosis (n)	118/121	71/68	60/65	0.53
Alc etiology	81 (34%)	50 (36%)	37 (30%)	0.41
Alcohol-related questions				
Asked about alcohol?	198 (83%)	105 (76%)	112 (90%)	0.09
Active drinker?	74 (31%)	44 (32%)	57 (46%)	0.42
Alcohol-related counselling provided?	260 (71%)		110 (88%)	<0.0001
In active drinkers only	*N = 74*	*N = 44*	*N = 57*	
AUDIT-10 performed? ‡ †	25 (35%)	15 (34%)	**41 (72%)**	<0.0001
AUDIT-10 score	10.3 ± 7.1	8.9 ± 8.1	8.7 ± 7.2	0.32
Alcohol-related interventions ‡†	7 (9%)	3 (7%)	**22 (39%)**	<0.0001
Missed opportunities ‡†	49 (65%)	29 (66%)	**16 (28%)**	<0.0001

‡p < 0.05 comparing Prosp vs Retro1, †p < 0.05 comparing Pros vs Retro2

Conclusion: Specific training and education about AUD to providers greatly improves rates of screening for & action taken as a result of detection of AUD & problem drinking. The familiarity of GI fellows with AUD-related instruments can be improved with training & placing AUDIT-10 in the EMR.

THU083

Temporal change in the plasma metabolome profile is indicative of outcome in severe alcoholic hepatitis

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Background and Aims: Severe alcoholic hepatitis (SAH) has a high mortality, and corticosteroid therapy is effective in reducing 28 day mortality in about 60% patients. There is limited data on the serial metabolomic profile of SAH patients on corticosteroid therapy and clinical outcomes (responder, R, Lille score <0.45 at day 7, or non-responder, NR) till 60 days.
Methods: We analyzed plasma metabolome at baseline, day 4,7,14 and 28 using ultra-high performance liquid chromatography and high-resolution mass spectrometry. Multivariate projection analysis identified metabolites in the discovery cohort (n = 35, R = 23, NR = 12) which were evaluated in the validation cohort of 100 patients (70 R, 30 NR).
Results: A total of 671 features were annotated by using metabolomic/spectral databases. SAH plasma showed significant increase in 181 metabolites linked to tryptophan metabolism, bile acids, butanoate metabolism, nitrogen metabolism and others, whereas significant decrease in 199 metabolites linked to glutathione metabolism, TCA cycle, pyruvate metabolism and others as compared to healthy subjects (FC ± 1.5, $p < 0.05$). Corticosteroid exposure for 4days increased plasma metabolites linked to tryptophan metabolism, bile-acids, nitrogen metabolism and reduced metabolites linked to sphingolipid metabolism, biosynthesis fatty-acids, glutathione metabolism, energy metabolism in NRs compared to R(FC ± 1.5,$p < 0.05$). Similarly, corticosteroid exposure for 7, 14 or 28days significantly increased plasma metabolites linked to inflammation; tryptophan, butanoate, arachidonic/leukotriene metabolism and decreased metabolites associated to antioxidant pathway (glutathione metabolism), biosynthesis of fatty acids and alternate energy pathways in NR (FC>1.5, $p < 0.05$). Increased plasma levels of 3-hydroxyanthranilate, L-kynurenine, 3-Indoleacrylic acid (tryptophan metabolism) and arachidonate, lecithin, leukotriene-C4, prostaglandin-B1 (arachidonic/leukotriene metabolism) significantly correlated to severity and mortality ($r > 0.4$; $P < 0.01$). Upon validation, baseline levels of L-kynurenine (OR, 2.1(1.5–3.2) Indoleacrylic acid (OR, 3.0 (2.4–8.2), lecithin (OR, 1.5(1.2–2.9) and prostaglandin B1(OR, 3.5(1.8–9.2) were the most significant predictors of non-response and non-survival (AUROC>0.80; $p < 0.05$) in our study cohort.
Conclusion: Corticosteroid over exposure has hazardous effect particularly on non-responsive patients. Temporal changes in plasma metabolome signatures associated with tryptophan and arachidonic/leukotriene metabolism can reliably predict at baseline steroid response and disease outcome in SAH patients.

THU084

Pharmacokinetics of DUR-928 in alcoholic hepatitis patients - a phase 2a study

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Background and Aims: DUR-928 is an endogenous small molecule that epigenetically modulates the gene expression of various nuclear receptors which play important roles in lipid homeostasis, inflammation, cell survival and regeneration. The potential use of DUR-928 as a treatment for acute organ injury, including alcoholic hepatitis (AH), has been demonstrated in multiple pharmacology studies in animal disease models. The primary objective of this Phase 2a study is to assess the safety and pharmacokinetics (PK) of DUR-928 in moderate and severe AH patients.
Method: The study is an open-label, multi-center, dose escalation safety/PK Phase 2a trial. All patients received DUR-928, at dose of 30, 90, or 150 mg, by intravenous infusion for 2 hrs on Day 1 and Day 4 (if still hospitalized), and were followed for 28 days. Part A of the study consisted of patients with moderate AH (MELD 11–20) and Part B included patients with severe AH (MELD 21–30).
Results: Total of 19 patients (12 severe AH, and 7 moderate AH) participated in the study. DUR-928 was well tolerated. The drug exposure (both AUC and C_{max}) in AH patients was dose proportional. Time to maximum drug concentrations (T_{max}) was at the end of 2 hour infusion. The half-life ($t_{1/2}$) of DUR-928 ranged from 4 to 6 hours. Mean clearance of DUR-928 was about 5–7 L/hr. PK parameters of DUR-928 were similar between the moderate and severe AH groups. Compared to PK parameters of DUR-928 in healthy subjects, there was a 2-fold increase in C_{max} and a 6-fold increase in AUC in AH patients at the same dose level. The clearance of DUR-928 was decreased by 80% in AH patients as compared to that in healthy subjects from an earlier study. In addition, encouraging efficacy signals, including early reduction from baseline of serum bilirubin levels and reduction of MELD on Day 28, and high treatment response rate (based on Lille score) were observed in the study (1, 2).

Conclusion: DUR-928 was well tolerated at doses tested in AH patients, including severe AH patients. Compared to the healthy subjects, AH patients had a much slower clearance, resulting in a 2-fold higher C_{max} and 6-fold higher AUC. However, the drug exposure was not affected by the severity of the disease.

References

1. McClain C. et al., *J. Hepatology*, 2019; 70(1), S834A
2. Hassanein T. et al., AASLD -2019 – Late Breaker A09

THU085

Alterations and role of bioactive lipid metabolites (oxylipins) in human and experimental ALD: associations with disease severity

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Background and Aims: Alcoholic liver disease (ALD) is a major contributor to total liver disease burden worldwide. ALD pathogenesis is not well understood and there is no effective therapy. Oxylipins, including epoxy- and dihydroxy-fatty acids (Ep-FAs and dihydroxy-FAs, respectively), are important signaling molecules that regulate various biological processes. Evidence suggests Ep-FAs are beneficial, anti-inflammatory lipid mediators, whereas the properties of dihydroxy-FAs are not well determined. In this study we aimed to: i) examine alcohol-induced alterations in plasma oxylipin levels in human ALD and ii) investigate the effects of dihydroxy-FAs in experimental ALD.
Method: Human studies: plasma lipidomic analysis was performed on 44 moderate (mAH) and severe (sAH) alcoholic hepatitis patients and 29 socially drinking healthy controls (HC). Animal studies: male C57BL/6 mice were subjected to a chronic-binge animal model of ALD (NIAAA model). Mice were administered either 8,9-DiHETE or a combination of 9,10-DiHOME and 12,13-DiHOME by i.p. injection once daily for two days prior to sacrifice. Liver injury, inflammation, and steatosis were evaluated. Primary mouse hepatocytes were treated with 8,9-DiHETE, 9,10-DiHOME, 12,13-DiHOME and baseline or palmitic acid (PA)-induced cell death was evaluated.
Results: Among dihydroxy-FAs, 8,9-DiHETE was elevated in both mAH and sAH compared to HC. 9,10-DiHOME was significantly elevated in mAH but not in sAH, while 12,13-DiHOME was similar in AH patients and HC. 9,10- and 12,13-EpOMEs were significantly decreased in both mAH and sAH compared to HC. Multivariable regression analysis revealed a moderate association between low 12,13-EpOME/high 8,9-DiHETE and plasma cytokeratin 18 M65 (CK18 M65), a marker of necrotic cell death in sAH ($r^2 = 0.3333$, $p = 0.0478$). *In vivo*, 8,9-DiHETE treatment modestly, while 9,10/12,13-DiHOME significantly, increased liver injury in mice as determined by elevated plasma ALT levels. Dihydroxy-FA treatment had minor effects on hepatic inflammation. *In vitro*, 8,9-DiHETE treatment significantly exacerbated PA-induced cell death of primary mouse hepatocytes, whereas 9,10-DiHOME, and 12,13-DiHOME had no effect on PA-induced or baseline cell death.
Conclusion: Plasma lipidomic analysis in human ALD identified distinct alterations of several plasma oxylipins between mAH and sAH. These bioactive lipid mediators may serve as novel biomarkers of ALD severity and represent therapeutic targets to prevent and/or attenuate progression of ALD. Dihydroxy-FAs, specifically 8,9-DiHETE, exacerbated liver injury in mice and increased PA-induced cell death in primary hepatocytes. Future studies are warranted to dissect the effects of individual dihydroxy-FAs in ALD.

THU086

Alcohol-induced liver injury is attenuated by human beta defensin in experimental ALD via improvements in the gut-liver axis

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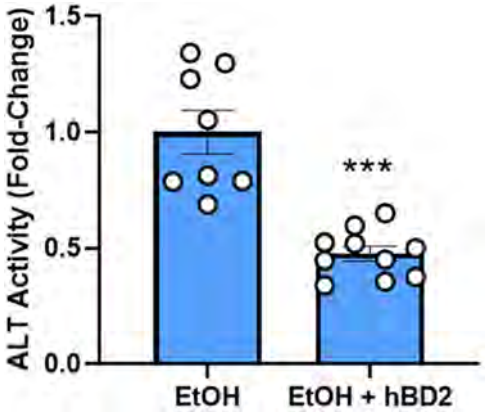
Background and Aims: Alcohol-induced liver disease (ALD) is associated with altered gut microbiota, compromised intestinal barrier functions, and endotoxemia, which further exacerbate liver damage. Currently, ALD has very limited effective therapeutic options. Defensins are small host peptides with bactericidal/immunomodulatory functions, which demonstrated beneficial effects in various animal models associated with inflammation. Here, we tested the hypothesis that human beta defensin 2 (hBD2) would attenuate ethanol-induced liver injury via improvement of gut barrier integrity and beneficial changes in the gut microbiome.
Methods: Male C57BL/6J mice were chronically fed ethanol (EtOH) for 5 weeks. During the final week, a subset of mice was administered 1.2 mg/kg hBD2 by oral gavage (8 treatments). Liver steatosis, injury and inflammation were evaluated. Pro-inflammatory lymphocytes were analyzed by flow cytometry in the intestine and mesenteric lymph nodes (MLN). Fecal microbiome was determined by 16S sequencing. Mouse intestinal enteroids were established and subjected to IFN-γ ± hBD2 treatment.
Results: Compared to EtOH-fed mice, EtOH + hBD2 treated animals revealed reduced hepatic steatosis, less liver damage as demonstrated by a 50% decrease in plasma ALT levels ($p < 0.05$), and a 60% decrease in the number of TUNEL-positive hepatocytes ($p < 0.05$). Further, hBD2 treatment reduced hepatic neutrophil numbers by 70% ($p < 0.05$) with a concomitant decrease in the expression of several proinflammatory genes, including chemoattractant cytokines, *Mip2a* and *Mcp1.* MLN-derived lymphocytes showed a decrease in pro-inflammatory Th1 ($CD4^+$ $IFN\gamma^+$) and Th17 ($CD4^+$ $IL17a^+$) cell populations by 55% and 33% respectively in EtOH + hBD2 compared to EtOH-fed mice. Fecal microbiome analysis revealed similar alpha diversity but a significant difference in composition, including increase in *Bifidobacterium* and decrease in *Akkermansia* in EtOH+hBD2 compared to EtOH treated mice. These changes have previously been linked to protection from and exacerbation of barrier dysfunction, respectively, in other liver disease states. Finally, small intestine enteroids treated with IFN-γ had decreased expression of the tight junction proteins, including *Ocln*, which was attenuated by co-treatment with hBD2.



Conclusion: Oral treatment with hBD2 of mice chronically fed EtOH significantly reduced liver injury and inflammation and led to favorable changes in the immune status and the gut microbiome. These results thus support hBD2 as a potential therapeutic agent for ALD acting via improvement of the gut-liver axis.

THU087

Type III interferon lambda derangements are associated with susceptibility to infection in alcohol-related liver disease

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Background and Aims: Alcohol-related liver disease (ALD) is characterised by impaired anti-bacterial immunity, driven by intestinal hyperpermeability and bacterial translocation. Type III interferons (IFN Lambda (L) 1/2/3/4) are important anti-pathogen cytokines with central roles in systemic and mucosal defenses. Polymorphisms in the genes encoding the IFNL proteins play an important role in chronic HCV infection. Here we explore the unknown role of IFNL in ALD, specifically examining neutrophils, liver, colon, plasma and assess the impact of single nucleotide polymorphisms (SNPs) in IFNL.
Method: IFNL1/2 and IFNL-receptor (R) expression were determined by qPCR in (A) Neutrophils challenged with/without *E. coli* from 7 patients with alcoholic hepatitis (AH), 13 patients with alcohol-related cirrhosis (ARC) and 12 controls (HC); (B) Colonic tissue from 10 ARC and 10 HC; (C) Liver tissue of AH/HC (GEOdata). Plasma IFNL1/2/3 were measured by ELISA in 42 AH, 26 ARC and 10 HC. Neutrophil phenotype and function were assessed by FACS post-IFNL treatment. Selected SNPs in IFNL were assessed in 804 AH, 305 ARC, 11029 HC and 2238 alcohol-dependent drinkers with no liver disease.
Results: Neutrophil IFNL1 was induced by *E. coli* in HC ($p = 0.001$) and ARC ($p = 0.005$), but was completely abrogated in AH. We observed intrahepatic IFNLR expression in AH/HC and IFNLR hyper-expression in ARC colon ($p = 0.003$). There was no intrahepatic or colonic gene detection for IFNL1 or IFNL2. The majority of AH patients (63%) were positive for plasma IFNL2/3 compared to ARC (43%). *In vitro* treatment with IFNL1 increased neutrophil TLR4 expression. No significant differences were identified in the IFNL SNPs between the four groups. However, in AH carriage of *IFNL4:*rs117648444 was significantly associated with infection at presentation, when adjusted for age and MELD score ($p = 0.028$).
Conclusion: Neutrophil anti-bacterial IFNL1 production is deficient in AH while carriage of *IFNL4:*rs117648444 may increase susceptibility to infection. We also show colonic IFNLR expression is increased in ARC, suggesting that this compartment, which is central to the immunopathogenesis in ALD, may be susceptible to IFNL-mediated modulation. Overall these findings point to widespread disruption of Type III interferon function in patients with ALD.

THU088

The role of PNPLA3, MBOAT7 and TM6SF2 during alcohol detoxification: different mechanisms of fibrosis and steatosis development

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Background and Aims: In genome wide association studies PNPLA3, MBOAT7 and TM6SF2 were identified as important risk genes for the development of alcoholic cirrhosis, however, their functions and molecular mechanisms are still poorly understood. We here present first data on the role of PNPLA3, MBAOT7 and TM6SF2 genotypes on liver stiffness (LS), steatosis (CAP) and inflammation during alcohol withdrawal.
Method: 763 patients with ALD which were hospitalized for alcohol withdrawal at Salem Medical Center between 2007 and 2018 were genotyped for PNPLA3 s738409, MBOAT7 rs626283 and TM6SF2 rs58542926 polymorphisms. All patients had routine laboratory, abdominal ultrasound and a transient elastography measurement (FibroScan) at admission. In 512 patients, data after 6.3 days of alcohol withdrawal was available.
Results: 71% of the patients were male, median age was 52 years, median BMI was 24.7 kg/m^2 and median alcohol consumption was 163 g/day. At admission, no difference between the genotypes of PNPLA3, MBOAT7 and TM6SF2 was seen regarding age, BMI, gender, alcohol consumption or transaminase levels. Significant differences were observed for PNPLA3 and MBOAT7 during alcohol detox. While MBOAT7 was associated with higher LS, no differences were observed between genotypes upon alcohol detoxification. In contrast, PNPLA3 caused clearly a delayed resolution of LS during withdrawal of alcohol due to inflammation. This could be recapitulated when looking at serum markers of liver inflammation. In a sub-analysis of n = 108 liver biopsies, inflammation was highly associated with PNPLA3 but not MBOAT7 and TM6SF2. More interestingly, PNPLA3 was associated with higher steatosis. No effect at all was seen for MBOAT7 on steatosis. For TM6SF2, no differences regarding LS, CAP or transaminases were seen between the genotypes before or after detoxification. A multivariate model confirmed that PNPLA3 was associated with steatosis and inflammation but not fibrosis. MBOAT7 was only associated with fibrosis/cirrhosis but not inflammation or steatosis.
Conclusion: These first genotype data on a "human alcohol knock-out" intervention underscore important difference between the three genes. PNPLA3 seems to primarily drive fibrosis through inflammation while MBOAT7 seems to have a direct effect on fibrosis. TM6SF2 showed no effect. Finally, alcohol detoxification could be a novel interventional approach to further dissect metabolic mechanisms and their associations with genotypes.

THU089

Loss of the resolvin D1-formula peptide receptor 2 signaling axis leads to pro-inflammatory transcriptional reprogramming in alcoholic liver disease

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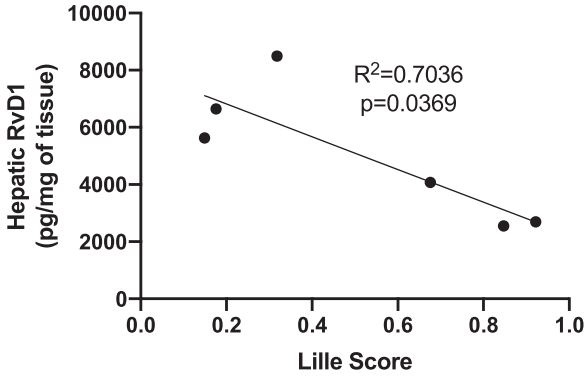
Background and Aims: Alcoholic liver disease (ALD) is a spectrum of liver disorders ranging from steatosis to steatohepatitis, and further progressing to fibrosis. Alcoholic Hepatitis (AH) is a clinical manifestation of severe liver damage often coinciding with systemic infection and inflammation. Formyl peptide receptor 2 (FPR2) is a mediator of inflammation resolution through interaction with the lipid-derived metabolite resolvin D1 (RvD1). In this study we aimed to investigate RvD1-FPR2-mediated transcriptional responses controlling the resolution of inflammation.

Method: For translational studies we utilized liver tissue samples acquired from AH patients (n = 7) and non-drinking controls (n = 12). Hepatic FPR2 and RvD1 levels were measured and used for regression analysis with markers of AH severity and prognosis (ABIC, MELD, and Lille Scores). The expression of signal transducer and activator of transcription 1 (STAT1) and early growth response 1 (EGR1), which regulate the transcription of inflammatory genes in response to bacteria and cytokines commonly increased in ALD/AH, were measured. For animal studies, female *Fpr2*$^{-/-}$ and WT mice were fed control or ethanol (EtOH)-containing diets *ad libitum* for 5 weeks and liver disease endpoints were measured. BMDMs isolated from naïve WT and *Fpr2*$^{-/-}$ mice were subjected to LPS + RvD1 in the presence or absence of EtOH.



Results: Hepatic RvD1 was negatively correlated with AH severity (ABIC, $R^2 = 0.78$; Lille Score, $R^2 = 0.70$). Hepatic FPR2 protein was reduced, while *STAT1* and its target gene guanylate binding protein 2 (*GBP2,* which releases intracellular LPS from bacteria and promotes pyroptosis) were significantly elevated in AH relative to controls. Hepatic *EGR1* was increased and positively associated with MELD score in AH ($R^2 = 0.7368$). Compared to WT, *Fpr2*$^{-/-}$ EtOH-fed mice had exacerbated EtOH-induced liver injury and inflammation. As compared to WT, *Fpr2*$^{-/-}$ mice fed EtOH had elevated levels of hepatic *Egr1.* LPS-stimulated WT but not *Fpr2*$^{-/-}$ murine macrophages had reduced *Egr1* and *Gbp2* after RvD1 treatment suggesting a potential mechanism of RvD1-FPR2-mediated resolution of inflammation.
Conclusion: The RvD1-FPR2 axis is compromised in AH associated with elevation of *STAT1* and *EGR1.* Genetic ablation of *Fpr2* exacerbates experimental ALD accompanied by elevated *Stat1* and *Egr1.* RvD1 mechanistically acts through negative regulation of STAT1 and EGR1 in a FPR2 dependent manner in murine macrophages.

THU090

High risk of futile over-referrals or late under-referrals among patients suspected of alcohol-related or non-alcohol-related fatty liver disease: real-world evidence reveal opportunities to optimize referral patterns to secondary care

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Background and Aims: We are facing an increased focus and expanded possibilities to treat alcohol-related (ALD) and non-alcohol-related fatty liver diseases (NAFLD). However, compensated cirrhosis and liver fibrosis are mostly silent disease and challenging to diagnose in primary care. Consequently, patients are frequently diagnosed at a symptomatic stage with decompensation. On the other hand, patients at risk of ALD and NAFLD that will never progress to advanced fibrosis may be referred for futile expensive and invasive investigations due to lack of applicable decision tools in primary care. We aimed to investigate the referral patterns, to a secondary liver center, of patients with suspected advanced fibrosis or related complications due to fatty liver disease.
Method: Audit of all referrals in 2016 and 2017 to a secondary care liver clinic. We evaluated the general physician's referral diagnosis from ICD-10 codes and electronic patient referral records and compared to the diagnostic conclusion made by experienced hepatologists after completing the liver clinic investigations. Two MD's reviewed all patients' electronic medical files. We labelled referrals as either: futile (no liver disease or mild fibrosis), timely (significant fibrosis or compensated cirrhosis) or too late referred (decompensated disease).
Results: 188 referrals from primary care or other non-hepatology departments were reviewed. 63% were male, mean age was 55 years. In total, 174/188 (92.5%) had a liver assessment in the department, 46.8% was returned to GP or the referring unit, and the other half, 50.0% remained in the department as a hepatology out-patient. One third (32.4%), of referred patients was judged as futile referred, furthermore, one third (29.7%) of referred patients was judged as referred to late. The last third of patients was judged as being timely referred to the department. If FibroScan was applied in all patients, the mean LSM was 5.6 kPa, 18.6 kPa, and 45.5 kPa if judged futile, timely and too late, respectively.
Conclusion: Only one-third of patients referred on suspicion of alcohol-related or non-alcohol-related fatty liver disease are correctly referred, in a timely manner. One-third of patients are futile referrals without liver disease, while another one-third is referred at the stage of decompensated cirrhosis.

THU091

Patients with alcoholic hepatitis present strong Th1 cellular immune responses to alcohol dehydrogenase related to impairment of the PD-1/PD-L1 pathway due to high circulating levels of soluble PD-1

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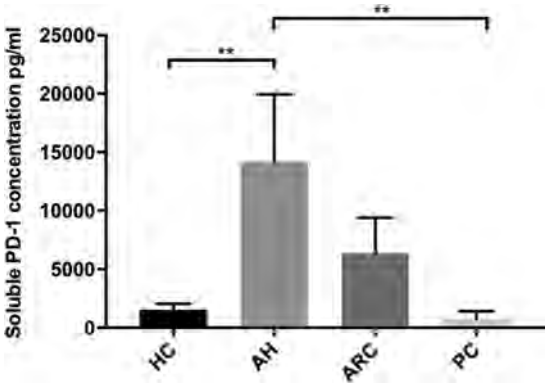
Background and Aims: Alcoholic hepatitis (AH) is characterised by florid hepatic inflammation, liver failure and high short-term mortality. We have previously reported that AH patients present strong cellular immune responses to alcohol dehydrogenase (ADH), with a predominant Th1 and a limited Th2 response. We have also observed that AH patients have a reduced frequency of suppressive PD-1 expressing CD4 T cells. The imbalanced cellular immune response to ADH is related to a defect in the PD-1/PD-L1 pathway, which negatively regulates T cells and is essential for the maintenance of peripheral tolerance. In this study, I aimed to evaluate the role of circulating soluble PD-1 (sPD-1) in patients with AH.
Method: PBMC and plasma were collected from 29 AH patients (20 female, median age: 43, range 25–63), 12 alcohol-related cirrhosis (ARC) patients (4 female, median age: 61, range 37–74), 9 pathological controls (PC) (NASH, PSC; 4 female, median age: 58, range 39–70), and 14 healthy controls (HC) (6 female, median age: 38.5, range 28–64). 1×10^5 cells/well were cultured with T cell stimulator and IL-2, with and without 10μM of 8 antigenic ADH peptides. Cells were cultured for 8 days in the presence or absence of anti-PD-1, anti-PD-L1 or combined anti-PD-1/PD-L1 neutralising antibodies. Cells were harvested and FACS used to determine T cell phenotype and frequency of cytokine producing T cells. Duplicate cell cultures were pulsed with 0.25 μCi/well ^{3}H-thymidine for 18 hours and harvested onto glass-fibre lined membranes. Thymidine incorporation was measured using a β-counter and expressed as the stimulatory index (SI). Proliferative responses were positive when $SI \geq 2.5$. Plasma (100 μl/well) was used to measure concentrations of soluble PD-1

using a sandwich ELISA according to the manufacturers standard protocol (DuoSet ELISA for human sPD-1, R&D Systems).
Results: In AH, positive PBMC proliferative responses were observed in the presence of ADH peptides, but not in their absence. Frequency of PD-1^{+ve}CD4^{+ve} lymphocytes was significantly higher in the presence of ADH peptides and no PD-1/PD-L1 blockade in HC than in AH (4.40 ± 0.54 versus 1.90 ± 0.26, p = 0.003). Mean baseline soluble PD-1 concentration was significantly higher in AH than in HC (14,205 ± 5741 versus 1536 ± 521.4 pg/ml, p = 0.0075) and PC (14,205 ± 5741 versus 755.9 ± 658.6 pg/ml, p = 0.0032). No other significant differences in sPD-1 were identified between groups.



Conclusion: Soluble PD-1 has been shown to counteract PD-L1 mediated suppression of CD4^{+ve} T cell proliferation in a number of autoimmune diseases. We have identified significantly higher levels of sPD-1 in patients with AH, who demonstrate inappropriate proliferative cellular immune responses to ADH. This may explain some of the beneficial effects of immune suppression in the treatment of AH. Further investigation of the role of sPD-1 is warranted in AH.

THU092

Differential roles of receptor interacting protein 3 and mixed lineage kinase like in murine models and patients with alcohol- and non-alcohol related liver disease

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Background and Aims: The intricate balance between cell death and pro-survival pathways is critical for regulating liver injury and inflammation during progression of ALD or NAFL/NASH. Previous work identified a critical role for *rip3,* a kinase regulating necroptotic cell death, in mediating chronic ethanol-induced, but not high fat diet-induced, liver injury in mice. In humans, RIP3 expression is low in healthy livers, but is increased in livers of patients with ALD and NAFL/NASH. However, very little data are available on direct comparisons of expression of the RIP1-RIP3-MLKL molecular machinery between patients with different etiologies of liver disease. Based on these data, here we investigated two questions: 1) is there a differential role for *mlkl*, the down-stream effector of RIP3 in the necroptotic pathway, in murine models of AH and NASH and 2) can RIP1-RIP3-MLKL be used as biomarkers to distinguish AH from NASH in patients.
Method: *Mlkl*$^{-/-}$ mice and their wild-type littermates were exposed to Gao-binge (acute on chronic) ethanol or high fat fructose and cholesterol diets (FFC). Liver tissue and plasma from patients with AH and NASH, as well as healthy controls (HC) were used for Western blot and ELISA.
Results: Despite the protective effect of *rip3*-deficiency in murine models of chronic ethanol exposure, *mlkl*-deficient mice were not protected from Gao binge-induced liver injury. In contrast, *mlkl*$^{-/-}$, but not *rip3*$^{-/-}$, mice were protected from FFC-induced liver injury. Western blot studies of liver samples from patients with NASH, AH, and healthy controls revealed distinct differences in expression patterns of phospho-RIP1, RIP1, RIP3, phospho-MLKL, and MLKL between HC, AH and NASH patients. pMLKL was higher in NASH vs AH and HC while phospho RIP1 was higher in AH vs NASH and HC. RIP1 and RIP3 concentration, assessed by ELISA in plasma, was also different between AH and NASH, with RIP3 increased in AH vs NASH and HC and RIP1 increased in NASH vs AH and HC. No differences in circulating MLKL were identified between AH, NASH and healthy controls.
Conclusion: Overall, the data from murine models indicate important non-canonical functions of RIP3 and MLKL differentially contribute to ethanol- and FFC diet-induced injury. Differential expression of proteins in the RIP1-RIP3-MLKL signaling pathway in liver and plasma from patients suggest that these differences might be leveraged to develop predictive models to distinguish AH and NASH.

THU093

High throughput plasma proteomics in 459 patients reveals patterns of protein dynamics in alcohol associated liver disease: a biopsy-controlled study

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Background and Aims: Alcohol-related liver disease (ALD) progresses through a range of histological lesions starting with alcohol-related fatty liver, to subclinical steatohepatitis, which drives accumulation of fibrosis, and ultimately cirrhosis. The plasma proteome changes corresponding to the severity of these disease entities remain to be elucidated. Mass spectrometry (MS) – based plasma proteomics holds great potential for biomarker discovery in an unbiased manner. We therefore investigated the plasma proteome in a cohort of 459 ALD patients compared to age-, BMI- and gender-matched healthy participants (HP, n = 136), to identify proteins differentially abundant between ALD and HP, and across the ALD spectrum, in dimensions of both steatosis, inflammation and fibrosis, and degrees of severity.
Method: Plasma samples were prepared on an automated liquid handling system. Proteome profiles were acquired on an LC-MS/MS platform using a hybrid BoxCar/DIA acquisition mode with a throughput of 30 samples per day. The resulting spectra were analyzed with Spectronaut™. Data analysis was done with Python scripts and the Perseus software.
Results: In total, we quantified 524 proteins. Three of six previously identified proteins associated with non-alcoholic fatty liver disease – PIGR, ALDOB, and LGALS3BP – were also upregulated in ALD compared to HP (by 158%, 95% and 64% respectively). There is a quantitative shift in proteome composition across biopsy-verified liver fibrosis stages, characterized by a decrease of liver-specific proteins including apolipoproteins, coagulation factors and organic substance transporters, and an increase of extracellular matrix proteins (ECM1, FBLN1, LUM, COL6A3, COL18A1, VWF, LGALS3BP, and TGFBI), transmembrane proteins and immunoglobulins. Of interest, we found dysregulation in components of Insulin Growth Factor (IGF) system, specifically a decrease of IGFBP3 and IGFALS (by nearly 50%), in contrast, to an increase in levels of IGFBP7 and

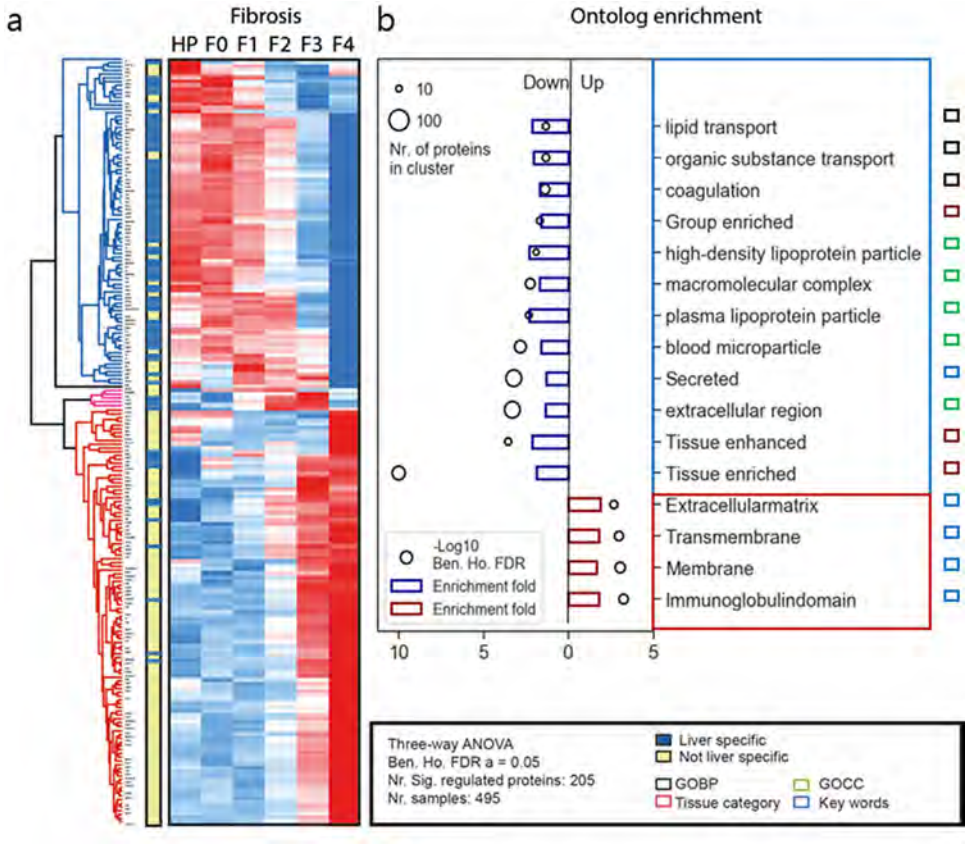

Figure: (abstract: THU093)

SPARCL1, both in a fibrosis stage dependent manner. In search of protein signatures representing liver fibrosis, inflammation and steatosis, we identified proteins correlating with severity of all three lesions. A prediction model based on six proteins (sensitivity, specificity, and MCC score of 0.86, 0.95 and 0.8) outperforms or is at par with the best-in-class markers and tests in detecting advanced liver fibrosis (ELF, FIB-4, APRI, PROC3, TF and 2D-SWE).

Conclusion: This study revealed novel patterns of protein dysregulation in alcohol associated liver disease. Proteins in these patterns likely play an active role in the process of fibrogenesis and reshaping the liver structure and function; they might consequently represent therapeutic targets. Prediction models based on pure proteomic features demonstrate similar accuracy as existing best-in-class biomarkers.

THU094

Defective gut adaptive immunity during early alcoholic liver disease

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Background and Aims: Alcoholic liver disease (ALD) severity is associated with increased microbial translocation (MT) and gut barrier dysfunction. Mucosal T cells, specialists of adaptive immunity, act as local gate keepers to protect against microbial invasion. However, their role during ALD in humans is still unknown. We aimed to assess the links between gut adaptive immunity, microbial translocation and ALD progression in alcohol use disorder (AUD) patients.

Method: Actively drinking AUD patients (n = 37) admitted to a rehabilitation program were included. Fasting blood and liver stiffness (kPa)/controlled attenuation parameter (CAP) measurements were obtained at admission and distal duodenal biopsies one day after.

Serum markers for gram– and gram+ microbial translocation (soluble CD14 and peptidoglycan recognition proteins (PGRPs), respectively) and liver cell damage (cytokeratin18 (CK18-M65)) were assessed by ELISA, duodenal immune cells by immunohistochemistry/flow cytometry.

ALD severity was clinically defined as: *non-progressive ALD*, i.e. no liver disease (normal AST, ALT, CAP < 250 dB/m, no fibrosis); simple steatosis (normal AST, ALT, CAP > 250 dB/m, no fibrosis) and *progressive ALD*, i.e. steato-hepatitis, *SH* (elevated AST, ALT, CAP > 250 dB/m, no fibrosis); steato-fibrosis (*SH* and significant fibrosis (kPa >7.6)).

Results: The duodenal mucosa of AUD patients was characterized by a reduction of CD3+CD8+ T cells compared to healthy subjects (n = 15). Within the CD8+ T cell pool, tissue-resident memory CD8+ (TRM; KLRG1-, CD103+) were significantly ($p < 0.05$) reduced. In addition, TRM of AUD patients had low CD69, a regulator of TRM tissue residency. Both changes (low TRM, low CD69) occurred independently from ALD severity. TRM inversely associated with PGRPs levels, a marker of gram+ translocation, suggesting their role in immunosurveillance.

By contrast, programmed cell death protein 1 (PD1), a master regulator of adaptive immunity, was down-regulated while the senescence marker CD57 was increased in CD8+ T cells of AUD patients with clinically progressive ALD and high CK18-M65, a marker of liver cell damage, compared to controls. This shift to the

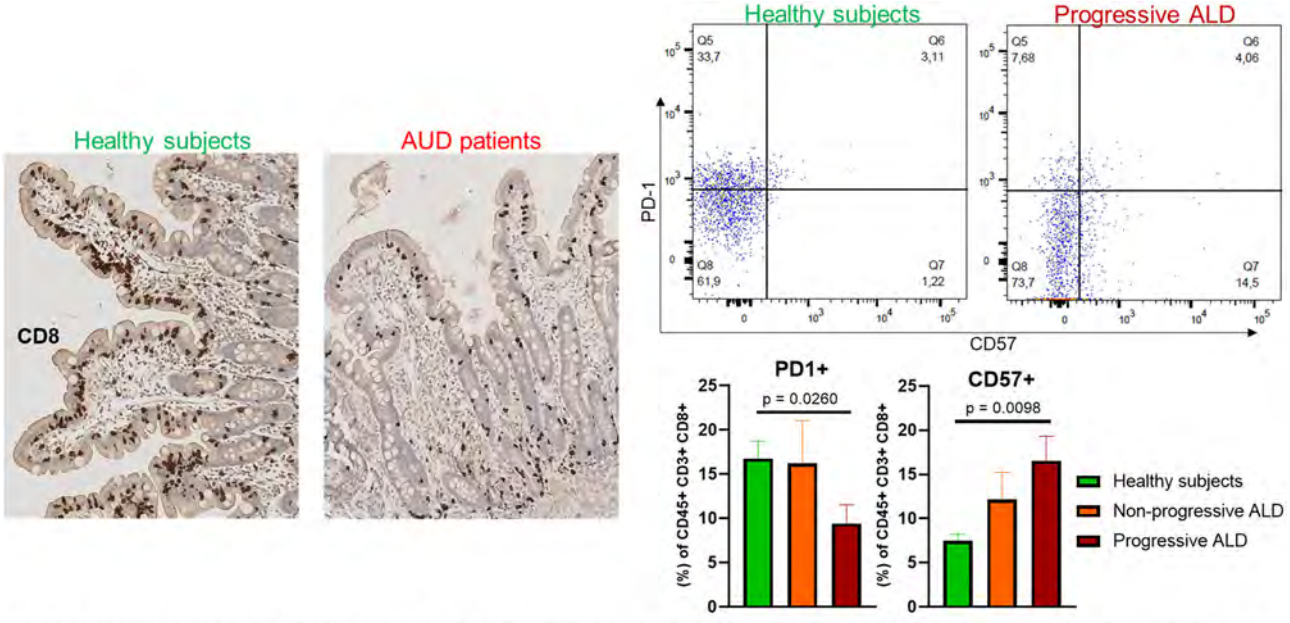

Figure: Representative duodenal sections stained for CD8 (left) of healthy controls and AUD patients; PD1 and CD57 down- and up-regulation ,respectively, (right) in progressive ALD

Figure: (abstract: THU094)

senescent phenotype (CD8+, PD1l$_{ow}$, CD57+) was associated with high sCD14, signing gram- translocation and points to an impairment of gut adaptive immunity.

Conclusion: In AUD patients, progressive ALD is linked to impaired gut adaptive immune responses which likely contribute to defective gut microbial immunosurveillance.

THU095

Metabolic and genetic risk factors predict advanced alcohol-related liver fibrosis regardless of drinking pattern

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Background and Aims: Excess drinking causes half of all liver-related deaths, but there is not a clear dose-response relationship between alcohol intake and development of cirrhosis. We hypothesized that genetic risk factors, insulin resistance and dyslipidemia may explain the heterogeneity in the severity of alcohol-related liver disease (ALD). Our aim was to improve precision of fibrosis staging in patients at risk of ALD due to harmful drinking.

Method: We performed a biopsy-controlled, cross-sectional study in patients with a history of excess drinking, with central scoring of liver biopsies for fibrosis stage and NAFLD activity score (NAS). We genotyped four polymorphisms (PNPLA3, TM6SF2, MBOAT7, HSD17B13), and determined the homeostatic model assessment of insulin resistance (HOMA-IR) from fasting insulin and blood glucose. We assessed dyslipidemia from plasma levels of triglycerides, HDL-, LDL- and total cholesterol. We performed multivariable proportional logistic regression to assess predictors of fibrosis while adjusting for age, sex, smoking, and whether patients were actively drinking or abstinent at inclusion.

Results: We included 325 patients (76% males, age 55 ± 11 years, 49% were abstinent from alcohol at inclusion, and 25% had advanced fibrosis). Insulin resistance was present in 54% of the patients, and worsened with every stepwise increase in fibrosis stage, while there was a global decrease in LDL, HDL and total cholesterol with increasing fibrosis (see Figure). Of the genetic polymorphisms, having one or two PNPLA3 or TM6SF2 risk alleles significantly increased fibrosis risk. In multivariable regression, insulin resistance was the strongest independent predictor for having a one-stage or more increase in fibrosis (OR = 3.22) followed by decreasing LDL-cholesterol (OR = 0.72) and presence of risk gene polymorphisms PNPLA3 (CG, OR = 1.61; GG, OR = 2.09) and TM6SF2 (CT, OR = 1.80; TT, OR = 8.15). In a subgroup analysis, HSD17B13 (TA) seemed to be protective against advanced fibrosis in patients with PNPLA3 CG or GG genotypes (OR = 0.56). Active drinking (OR = 4.52), insulin resistance (OR = 3.83) and PNPLA3 risk allele (OR = 1.59) were independent predictors of a one-point or more increase in the NAFLD activity score (NAS). All shown ORs have $p < 0.05$.

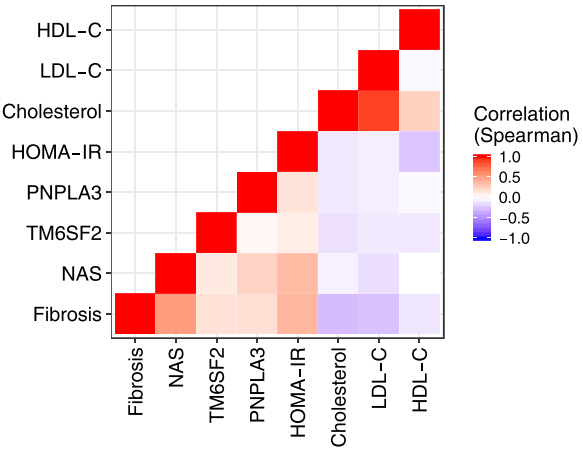

Figure: Heatmap showing the Spearman correlations between selected markers of liver disease, liver-related single-nucleotide polymorphisms,

glucose- and lipid metabolism. HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; NAS, NAFLD activity score; Fibrosis, Kleiner fibrosis score.

Conclusion: Metabolic changes and genetic risk polymorphisms are highly prevalent and substantially increase the odds of having advanced liver fibrosis in alcohol-related liver disease, regardless of drinking pattern.

THU096

The Stanford integrated psychosocial assessment for transplantation (SIPAT) is an effective tool at identifying limited sobriety candidates with alcohol-related liver disease and low risk of relapse

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Background and Aims: Carefully selected patients with alcohol related liver disease (ALD) and less than six months of sobriety have acceptable post-liver transplant (LT) outcomes. A fair, equitable system to identify ALD patients that are unlikely to recover hepatic function with sobriety along with a low risk of alcohol relapse remains a challenge. Our study assesses the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) in identifying suitable LT candidates with limited sobriety.

Method: Single centre retrospective study of all LT recipients (LTR) with ALD from 2015–2019. SIPAT is a validated tool performed being used at our center since 2013. The score ranges from 0–80, with a lower score indicating a favourable psychosocial profile. An official policy for limited (<6 months) sobriety was implemented in 2018 to include psychiatric and addiction medicine consultation and a post-LT relapse prevention plan (RPP). Post-LT outcomes were assessed and compared between those with and without limited sobriety.

Results: Of 103 LTR, mean age was 53.6 years, 75% male, 45% Caucasian and 38% Hispanic origin. 16 LTRs had limited sobriety. Marital status, education background and socioeconomic status was similar in those with limited and extended sobriety. Median SIPAT score was 27 and did not differ between groups ($p = 0.31$). LTRs with limited sobriety were more likely to be presenting with first decompensation ($p = 0.01$) and hepatorenal syndrome ($p < 0.01$). Rates of graft rejection (29%), infection (26%), and 1-year survival (88%) were similar in both cohorts. Alcohol relapse occurred in 7% and33% of LTRs returned to work. Of 7 LTRs with relapse, 5 had sustained use and only 1 was in the limited sobriety cohort. Factors associated with relapse included pre-LT renal replacement therapy ($p = 0.01$) and coexisting psychiatric illness ($p = 0.02$). Relapse was associated with failure to comply with immunosuppression ($p = 0.04$), relapse prevention plan ($p < 0.01$) and support system breakdown ($p = 0.03$). Presence of psychopathology on SIPAT assessment was significantly associated with relapse (OR 6.4, 95% CI 1.7–34.9, $p = 0.03$). The limited sobriety LTR group had excellent outcomes, 81% were adherent to their implemented RPP, with negative toxicology screens, follow-up with addiction medicine and regular attendance at support groups. Return to work rates for the limited sobriety group were significantly higher (69%) compared to those without limited sobriety (26%) ($p = 0.001$).

Conclusion: LT for ALD with limited sobriety achieves excellent outcomes in carefully selected patients. The previously validated psychosocial evaluation tool, SIPAT may be a useful adjunct in the selection of LT candidates with limited sobriety and should be studied prospectively.

THU097

The development and severity of alcoholic hepatitis is associated with decreased intestinal microbiome-derived secondary bile acid isoursodeoxycholic acid

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Background and Aims: Nonalcoholic steatohepatitis (NASH) is associated with specific perturbations in bile acid profiles linked to disease severity [*Hepatology*, 2018 Feb;67(2):534–548]. It is not known if similar changes are also seen alcoholic hepatitis (AH). *Aims:* (1) To define the changes in bile acid profile induced by (A): heavy alcohol consumption (B): moderate and severe AH (MAH, SAH defined by MELD ≤ or >20). (2) To define the relationship of changes in bile acid profile to severity of AH.

Method: Patients with moderate and severe AH (MAH, SAH - defined by MELD score ≤ or >20 respectively) were compared to controls without overt liver disease (normal LFTs, hepatic imaging and liver stiffness) who drank heavily (HC) and normal controls (NC) without an alcohol use disorder or overt liver disease. Bile acid profiles in plasma and feces were quantified by LC/MS. Correcting for false discovery, significant differences in pair-wise comparisons were established by Welch two-sample t-test ($p < 0.05$).

Results: 73 patients were studied (NC: 20, HC: 20, MAH: 11, and SAH: 22). The groups were matched by demographic profiles. The mean MELD scores for MAH and SAH were 15 and 27. ***A: Changes induced by heavy alcohol consumption (HC vs NC):*** Total primary bile acids were increased in plasma; both glycine and taurine-conjugated cholic acid and chenodeoxycholic acid (GC, GCDC, TC, TCDC) were increased ($p < 0.05$). Sulfated GCDC was also increased ($p < 0.01$). The unconjugated secondary bile acid deoxycholic acid (DCA) was reduced ($p < 0.05$), but both glycine and taurine-conjugated ursodeoxycholic acid (GUDCA, TUDCA) were increased ($p < 0.05$). ***B: Changes induced by AH (HC vs MAH/SAH):*** Total primary bile acids were increased in plasma but not in stool; both glycine and taurine-conjugated cholic acid and chenodeoxycholic acid (GC, GCDC, TC, TCDC) were increased ($p < 0.001$). There was isolated increment in fecal TCDC ($p < 0.005$). Unconjugated and glycine- and taurine-conjugated secondary bile acids were decreased in stool and in plasma ($p < 0.05$). Of note deoxycholate (conjugated or unconjugated) which is increased in NASH was not increased in AH. However, plasma taurolithocholic acid and glycolithocholic acid were both increased significantly in AH ($p < 0.05$); these were mostly in sulfated form. ***C: Changes related to severity of AH (MAH vs SAH):*** There was a stepwise increase in C4 from HC to MAH to SAH ($p < 0.005$ for both). Also, the intestinal microbial metabolite isoursodeoxycholic acid was progressively and significantly decreased from NC to HC to MAH to SAH. There was also a trend for decreased UDCA and 7-keto deoxycholic acid in stool in SAH (p 0.05–0.1).

Conclusion: AH promotes bile acid synthesis. Alcohol consumption increases endogenous UDCA synthesis. The development and severity of AH is related to a progressive decline in the hydrophilic, gut microbiome-derived secondary bile acid isoursodeoxycholic acid.

THU098

H2O2, the major reactive oxygen species produced during alcohol metabolism in liver induces autophagy without involving mTOR

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Background and Aims: Alcohol-mediated reactive oxygen species (ROS) formation in the liver, mainly H_2O_2, contributes to disease progression and eventually hepatocellular carcinoma development in patients with ALD. Enhancement or activation of autophagy, with the suppression of mTOR signaling, is likely to play an important role in early stages of the alcoholic liver disease (ALD). However, with the progression of the disease, the expression of mTOR increases dramatically leading to the suppression of autophagy. According to recent literature, this is accompanied with significant hepatic lipid accumulation and iron deposition as well as inflammation under persistent alcohol exposure. It is also known, that H_2O_2 is involved in the regulation of autophagy in both acute and chronic ALD models, however, the exact underlying molecular mechanisms are still unclear. Therefore, we investigated in vitro and in vivo by using alcohol mouse model alterations in mTOR signaling as well as downstream effects induced by H_2O_2 and low oxygen tension.
Method: Huh7 hepatoma cells and VL-17A cells (stably transfected with CYP2E1 and ADH) were cultured with the GOX/CAT system, which allows an independent control of hydrogen peroxide as well as oxygen levels, in combination with different doses of ethanol. LC3B, p62, mTOR and autophagy related proteins (e.g. AMPK, AKT, STAT3) were analyzed by western blot. Same analyses were performed in liver tissues of C57BL/6 mice treated with acute (alcohol binge) and chronic ethanol (20% ethanol in the drinking water) for 4 weeks (n = 4).
Results: H_2O_2 significantly increased LC3B activation and this effect could be efficiently blocked by N-acetyl cysteine (NAC), which is a ROS scavenger. Interestingly, even though the LC3B activation was increased by H_2O_2, the m-TOR expression was not suppressed as normally expected. Co-treatment of hepatoma cells with H_2O_2 and the mTOR inhibitor Rapamycin led to an increased autophagic flux as compared to single H_2O_2 and Rapamycin treatment. The in vivo experiments showed a combined activation of LC3B and suppressed p62 and AKT levels as well as enhanced p-AMPK expression in the livers of the acute alcohol group. In contrast, mice exposed to chronic alcohol showed blocked autophagic flux with dramatically increased LC3-I and p62 levels.
Conclusion: Our findings underscore an important role of H_2O_2 in regulating autophagy during acute and chronic alcohol ALD exposure. Further studies will be needed to address the differences between acute and chronic alcohol-mediated effects as well as to identify H_2O_2-induced signaling pathways that regulate autophagy.

THU099

Early diagnosis of alcohol-related liver disease and timely intervention: the role of alcohol care teams

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Background and Aims: Mortality due to Alcohol related liver disease continues to rise. The National Health System (NHS) in the UK spends £3.5 billion a year on alcohol related problems, of this cost 78% is for Hospital based care yet patients with Alcohol related Liver disease usually present late with complications. Alcohol care team (ACT) was established in October 2018 at the King's College Hospital, London with an aim to reduce alcohol related hospital admissions and readmissions and to improve patient care. The team comprises of a Consultant Hepatologist, Consultant Addiction Psychiatrist and 6 nurses.
Method: 1700 patients with Alcohol use disorder (AUD) presented to the ACT between October 2018–19. Alcohol harm was assessed using the Alcohol Use Disorders Identification Test (AUDIT). Inpatients are jointly reviewed by an Addiction Psychiatrist and the Hepatologist. Patients were assessed for signs of chronic liver disease, offered brief/enhanced motivational intervention +/– anti relapse medication and sign posted to the community services. More recently, patients presenting with AUD in the Emergency Department (ED) and the Acute medical wards are offered bedside Fibroscan to screen for Liver disease.
Results: 30% (500/1700) had spectrum of Liver disease, 51% (253/500) had cirrhosis, 10% (27/253) had decompensated Liver disease; 49% (247/500) were noted to have fatty liver on ultrasound. Only a third of patients (84/253) with cirrhosis were known to the Hepatology team despite frequent attendances to the Hospital. Following the involvement of ACT more than 70% of the patients are now attending the Liver outpatients (OPA) and successfully achieving abstinence/harm reduction.
Fibroscan was offered to n = 46 with no known Liver disease. 35/46 had an AUDIT score>20 (dependence), the median Liver stiffness measure (LSM) = 11.5. 5/46 had an AUDIT score 15–19 (higher risk), the median LSM = 8, 6/46 had an AUDIT score 8–15 (increasing risk), the median LSM = 4.2 (Fig 1). Though the patients require a repeat FS after a period of abstinence, its implementation has led to abstinence/harm reduction and influenced their engagement with Liver services. The above interventions have enabled the patients to link in with the

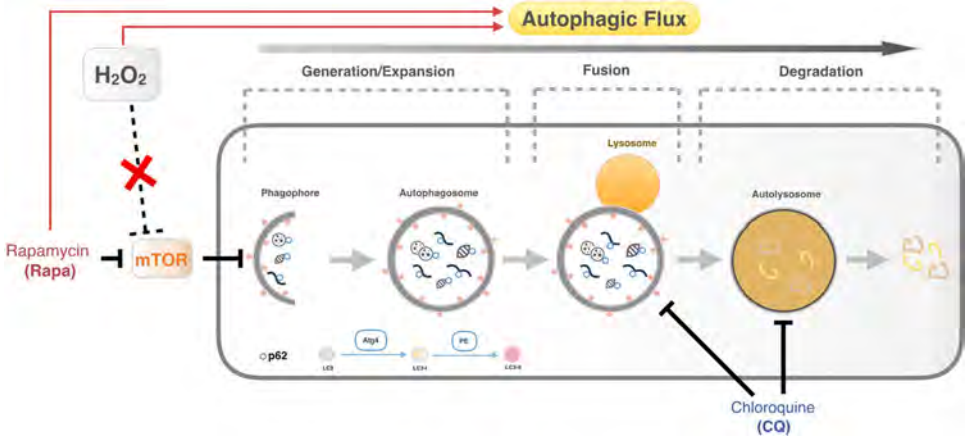
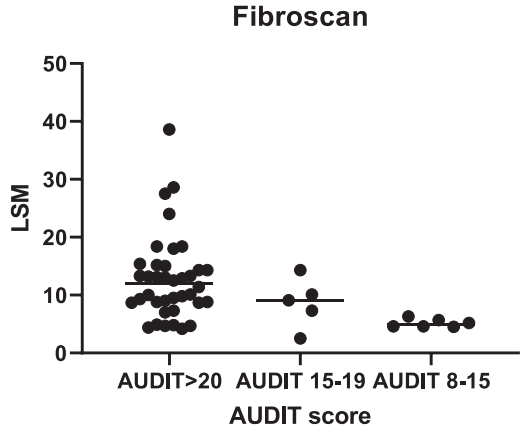


Figure: (abstract: THU098)

Community and Hospital services thereby reducing Hospital admissions and readmissions



Conclusion: Multidisciplinary approach in the management of AUD in patients with Chronic Liver disease is imperative in preventing further progression of Liver disease and associated complications.
Though recently established, early identification of Liver disease using Fibroscan in patients with AUD is feasible at the first point of contact.
Early identification of Liver disease and timely intervention is vital in preventing the progression to chronic Liver disease.
High LSM readings are found in patients with high AUDIT score but we need more data to establish this correlation.

THU100

A scoring system to predict infection in alcohol-associated hepatitis

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Background and Aims: Alcohol-associated Hepatitis (AAH) is a serious form of liver injury with mortality as high as 30–40% at 28 days. Multiple factors contribute to poor outcomes in this population, and superimposed infections are likely to increase mortality. Predicting the risk of infection in patients admitted with AAH can be challenging and the role of prophylactic antibiotics remains unclear. We aimed to identify predictors of infection in patients with AAH and create a scoring system to risk stratify these patients at the time of admission.
Method: We performed a retrospective analysis of patients admitted to two independent tertiary centers with a diagnosis of AAH from 1998–2016 (test cohort, n = 252). The diagnosis of AH was confirmed by manual chart review using the recent NIAAA definition. Infections were categorized by location and time of diagnosis: hospital-acquired infection (48 hours after admission until discharge) and post-hospital infections (up to 6 months after discharge). Patients who presented with community-acquired infection were excluded from analysis.
Results: The cohort was 66% male and the median age was 48 (21–83). Corticosteroids were used in 33% of all AAH patients. The overall infection rate in our cohort was 27%. Of those with infections, 46% were hospital acquired and 54% were acquired post-hospitalization. Variables found to be significant risk factors for bacterial infection included the presence of ascites on admission (HR 2.06), corticosteroid administration (HR 1.70), MELD greater than 23 (HR 2.61) and white blood cell count on admission per point (HR 1.02) (Figure 1). A scoring system was developed to predict infection at 7, 30, and 180 days from initial presentation: 1.03*MELD + 1*WBC + 1.61 (if ascites present) + 1.28 (if corticosteroids given) (Figure 2).

	HR (95% CI)	p-value
MELD on Admission (per point)	1.05 (1.02, 1.09)	0.002
Ascites on admission (Yes vs No)	2.06 (1.26, 3.36)	0.004
WBC on Admission (per 1 unit)	1.02 (1.00, 1.05)	0.048
Corticosteroids (Yes vs No)	1.70 (1.05, 2.75)	0.031

	Risk of infection within:		
Score	7 days	30 days	180 days
15	3.4%	11.0%	19.1%
20	3.8%	12.3%	21.2%
25	4.3%	13.7%	23.5%
30	4.8%	15.3%	26.0%
35	5.4%	17.0%	28.8%
40	6.1%	18.9%	31.7%
45	6.8%	21%	34.9%
50	7.6%	23.3%	38.3%
55	8.5%	25.8%	41.9%
60	9.5%	28.5%	45.7%
65	10.7%	31.4%	49.7%
70	11.9%	34.6%	53.9%
75	13.3%	38%	58.1%
80	14.8%	41.5%	62.4%
85	16.5%	45.3%	66.8%

Conclusion: In an analysis from a multi-center cohort of patients admitted with AAH we found that MELD score, ascites, WBC count, and the use of corticosteroids were significant predictors of the development of bacterial infection. In addition, we have developed a scoring system to help stratify patients at risk of infection within the following 180 days. In the future, we hope to utilize this scoring system to help dictate the use of prophylactic antibiotics in patients with AAH.

THU101

Unexpected protective role of the chemokine lix after Gao-binge ethanol feeding in mice

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Background and Aims: Members of the chemokine system of ligands and receptors are implicated in the progression of Alcohol-associated Liver Disease (ALD). The goal of the current study was to determine if there are pathophysiological changes to the entire system of chemokines in ALD patients and following Gao-Binge ethanol feeding in mice to identify novel therapeutic targets associated with the chemokine system.
Method: Weighted gene correlation network analysis (WGCNA) was performed on microarray data from livers of healthy control and alcoholic hepatitis (AH) patients (GSE28619) to evaluate the coordinated expression of chemokines in livers of ALD patients. Mice were fed ethanol per the Gao-binge protocol and chemokine release was determined in plasma. Primary murine hepatocytes were used for mechanistic studies.
Results: The top 50% differentially expressed genes (3789) of GSE28619 were selected to construct the co-expression network for WGCNA. The correlation between Module eigengenes (MEs) and the clinical traits was calculated to identify the modules that are highly related to AH. Modules with absolute values of MEs above 0.9 were selected. Members of the C-X-C chemokine family, including *CXCL1, CXCL2, CXCL5, CXCL6* and *CXCL8*, were highly associated with AH as compared to healthy controls. In mice, the mouse-specific C-X-C chemokine LIX, a homolog to human CXCL5 and CXCL6, was uniquely

increased in the plasma as compared against all other circulating chemokines after Gao-binge feeding. Surprisingly, anti-LIX treatment exacerbated ethanol-induced liver injury as measured by ALT and expression of *Ccl2, Cxcl1, Cxcl2* and *Il-1Beta* mRNA as compared to IgG controls. Expression of Cxcl1, Ccl2 and LIX protein was also increased in liver homogenates. Since hepatocytes are known to release these chemokines, LIX was neutralized in primary hepatocyte cultures. Consistent with the *in vivo* data, LIX neutralization led to increased release of chemokines Ccl2, Cxcl1, Cxcl2, and LIX into cell culture supernatants.

Conclusion: The C-X-C chemokines are strongly associated with ALD progression. The mouse homolog of human CXCL5 and CXCL6, LIX, is prominently upregulated after Gao-Binge feeding in mice and likely participates in a negative feedback loop to prevent excessive inflammation in the liver. This study suggests that chemokine signaling through hepatocytes might regulate expression inflammatory genes in ALD.

THU102

Shedding light on BASH: a novel experimental model of advanced liver damage

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Background and Aims: Based on recent clinical studies it has been suggested to refer patients with an intermediate alcohol drinking pattern and with signs of metabolic risk, including obesity and type 2 Diabetes Mellitus, i.e. clinical features of **b**oth alcoholic and non-**a**lcoholic **s**teato**h**epatitis as **BASH.** Yet, BASH is not well described and presents a large grey area in the field of Hepatology with a huge unmet need of pre-clinical and clinical studies as well as new innovative experimental animal models.

Method: C57BL/6 female mice received 10%v/v alcohol in sweetened drinking water in combination with a Western diet (WD) up to 23 weeks (BASH model). Mice receiving either only sweetened alcohol or only WD were used as controls. Serum markers of liver damage, liver and epididymal white adipose tissue (eWAT) histology, hepatic inflammation and fibrosis progression were analysed in detail.

Results: Animals fed with our novel experimental BASH model elicited a significant increase in the body-mass index (BMI) accompanied by a pronounced hypertrophy of adipocytes, as well as massive infiltration of macrophages, and robust collagen deposition in Ewat (Fig. 1A).

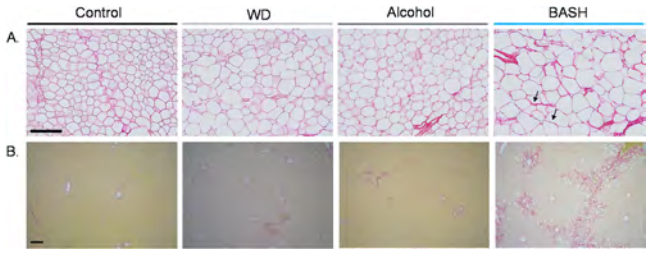

Figure 1. Sirius Red staining of eWAT (A) and liver tissue (B).

Moreover, progressive metabolic perturbations characterized by hypercholesterolemia and fasting hyperglycemia were found in the BASH group. In our experimental model, alcohol potentiated the effect of WD with regard to dramatic hepatomegaly, hepatocyte enlargement, profound hepatic steatosis and drastically increased levels of hepatic triglycerides. Significant liver damage was characterized by elevated plasma ALT and LDH levels, positive TUNEL staining and compensatory hepatic proliferation.

Notably, the BASH feeding also resulted in significant lobular inflammation and intrahepatic accumulation of CD45, CD11b and F4/80-positive immune cells and upregulated mRNA expression of TNFα and CCl2.

Importantly, BASH - mice exhibited advanced hepatic fibrosis, collagen accumulation, activation of hepatic stellate cells (HSC) and upregulation of Collagen IA1 and MCP-1 transcripts (Fig. 1B).

Conclusion: Our novel model of BASH displays enhanced obesity, glucose intolerance, liver damage, prominent steatohepatitis and hepatic fibrosis, as well as inflammation and fibrosis in the eWAT tissue. Altogether, the BASH model perfectly mimics all histological, metabolic, transcriptomic gene signatures of human BASH and therefore it can facilitate preclinical development of therapeutic targets in the future.

THU103

Duration of alcohol abstinence as a predictor of alcohol relapse - the more the better?

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Background and Aims: Alcohol abstinence is the mainstay of treatment of alcohol-related disorders, particularly liver disease. Heavy drinkers that achieve durable alcohol abstinence significantly reduce their risk of developing liver disease, and might not need surveillance. Furthermore, treatment modalities such as liver transplantation have been denied to patients with alcohol use disorder, unless these patients undergo a 6 months period of alcohol abstinence. However, there is no solid scientific evidence supporting the role of duration of alcohol abstinence as a predictor for alcohol relapse. We aimed to evaluate the risk factors for alcohol relapse in patients with alcohol use disorder.

Method: 123 long-term heavy alcohol consumers without chronic liver disease were prospectively recruited from a rehabilitation clinic in 2002 and followed until 2018. Alcohol consumption pattern and abstinence were registered.

Results: Baseline alcohol consumption was 330 ± 222 g/day for 25 ± 13 years, 65% being abstinent for 6 ± 27 months. The mean follow-up was 14 ± 3 years. Alcohol relapse occurred in 53%. Relapse did not associate with gender, amount, years or lifelong alcohol intake, binge drinking, type of beverage consumed, presence of alcoholism stigmata or family history of alcoholism or liver disease. There was a trend to higher GGT level at baseline in those with alcohol relapse (96 ± 161 *vs.* 58 ± 93 IU/L, p = 0.093). Relapse negatively associated with baseline abstinence duration: OR 0.306 [0.142–0.685] for 1-month and 0.276 [0.114–0.668] for 6-months. However, that association was weak and similar for 1 or 6-months abstinence (AUROC 0.362 ± 0.050, p = 0.009 and 0.385 ± 0.052, p = 0.029, respectively).

Conclusion: Alcohol consumption relapse was only weakly associated with the duration of baseline abstinence, and 6 months abstinence did not perform better than 1 month. These results

suggest the need for better predictors for alcohol relapse, reinforcing the concept that the 6 month abstinence rule for liver transplantation, although useful to allow spontaneous recovery of liver function, is not a good predictor of sustained abstinence.

THU104

Alcohol-related liver cirrhosis patients have higher-disease severity, one-year morbidity and mortality after index hospitalisation- followup of a cohort of 5,138 patients

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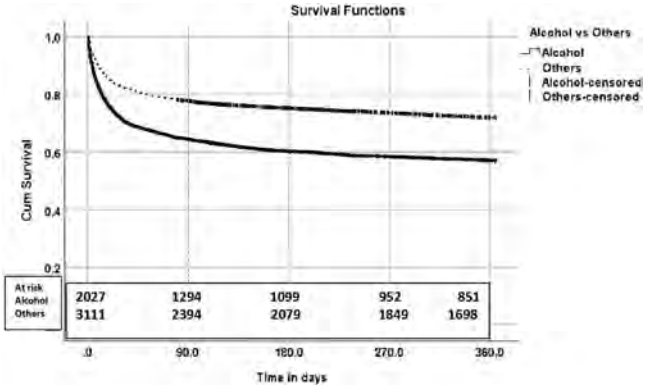
Background and Aims: Liver cirrhosis (LC) is becoming an increasingly important cause of morbidity and mortality globally. Survival decreases following decompensation and reduces further, with every hospitalization. We studied the clinical profile and long-term outcomes comparing alcohol related LC with all non-alcohol etiologies (viral hepatitis, NAFLD, etc,).
Method: LC patients hospitalized between January, 2010 to June, 2017, with atleast ≥ 1year follow-up were included. Logistic regression was used to measure odds-ratios and Poisson regression for incidence risk ratios for alcohol related LC outcomes.
Results: 5138 LC patients [age 49.8 ± 14.6 yr, male 79.5%; alcohol 39.5% (n = 2027), Child A:B:C-11.7%:41.6%:46.8%] from their index hospitalization were analysed. The median time from diagnosis of cirrhosis to index hospitalization was 2(0.2–10) years. During the one year follow-up, 1707(33.2%) patients died; 1248(24.3%) during index hospitalization; 59.5% (2316/3890) of the survivors, required at least one readmission in the following year, with additional mortality of 19.8%. Alcoholic cirrhotics compared to non-alcohol etiologies were significantly more often ($p < 0.001$) male (97.7% vs. 67.7%), younger (40–50 group: 36.2% vs. 20.2%) with higher liver related complications at baseline [sepsis (20.3% vs.14.9%), ascites (82.2% vs. 65.9%), spontaneous bacterial peritonitis (21.8% vs. 15.7%), hepatic encephalopathy (41.0% vs.25.0%), acute variceal bleed (32.0% vs.23.7%)] and acute kidney injury (30.5% vs. 19.6%) with greater disease severity CTP (10.6 ± 2.0 vs. 9.0 ± 2.3) and higher MELD scores (21.49 ± 8.47 vs. 16.85 ± 7.79). Mortality was higher in alcohol etiology compared to non- alcoholics with a lower one year probability of survival (57.7% vs. 72.7%, $p < 0.001$).



Conclusion: A fourth of cirrhosis patients die during the index hospitalization and 60% require at least another rehospitalization in the following year. Alcoholic cirrhosis present at younger age with more severe liver disease with higher morbidity and mortality than patients with other etiolgies of cirrhosis and therefore require greater attention.

THU105

Comparitive hepatic proteome analysis in low and high dose ab libitum alcohol mice model of liver injury

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Background and Aims: In most previous animal models of alcohol liver disease (ALD), how drinking pattern affects initiation and disease progression is not fully explored. In these models there has been a lack of comparison with hepatic proteome variations as expressed over time with low and high dose of ethanol. We aim to capture the alcohol induced proteomic variations and associated liver injury and repair proteins in longer duration ad libitum mouse model.
Methods: C57/B6 male mice (aged 6–8 weeks) fed with *ad libitum* 5% or 25% EtOH in the Lieber-DeCarli liquid diet daily for 12 weeks. Liver histology, liver injury marker and biochemical parameters were evaluated. Label free quantitative proteomic analysis by high resolution mass spectrometry was then performed. Student's two-tailed unpaired t-test was used to determine statistical significance followed by pathway analysis.
Results: At 12-weeks H&E staining showed marked steatosis in ethanol fed mice with increase in expression levels of liver injury markers in mice fed 25% EtOH compared to controls. We identified total of 4474 proteins. Out of 476 differentially expressed proteins (DEPs) in 5% EtOH fed mice 251 were up and 225 were down-regulated. Whereas in 25% EtOH fed mice group, Of the 1107 DEPs 154 were up and 953 downregulated (1.5FC; $p < 0.05$). Bioinformatic analysis of upregulated proteins showed unique pathways linked to processes of inflammatory-mediators, HIF1 signaling, arachidonic acid metabolism whereas unique pathways associated to down-regulated proteins were amino-acid, P450 xenobiotic metabolism, and oxidative phosphorylation ($p < 0.05$). Moreover, mice fed 25% EtOH displayed down-regulation of AMPK regulated proteins, but increased calcium-binding protein (CAB39) and decreased phosphoenolpyruvate carboxykinase 2, (PCK2) compared to 5% EtOH (FC> ±1.5; $p < 0.05$). A significant number of proteins were identified in 25% EtOH group were linked to inflammatory processes, most prominently damage associated proteins and neutrophil associated proteins. Moreover, this study identified target proteins such as Apolipoprotein A-II (Apoa-2), peroxisomal acyl-coenzyme A oxidase-1 (Acox1), ATP-binding cassette-3 (Abcd3), and damage associated high mobility proteins (Hmgn5). In high dose of EtOH fed mice the identified proteins correlated with α-SMA, TGF-β ($r^2 > 0.74$, $p < 0.05$).
Conclusion: Hepatic proteome analysis revealed dose dependent effect in EtOH-induced steatosis and liver injury suggesting a linkage between lipid metabolism, arachidonic acid metabolism and AMPK signaling, thus highlighting the effect of low and high dose ethanol intake paradigms on liver injury outcomes.

THU106

Neuro-immunological pathway alters the phenotype of bone marrow F4/80+CD11b+ macrophages during chronic alcohol consumption

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Background and Aims: Bone marrow (BM) is an important organ for immunity and haematopoiesis. In alcoholic liver disease, infiltrated macrophages from BM cause liver damage through inflammatory responses. However, the precise mechanism of phenotypic changes in macrophage by alcohol have not been well elucidated in BM yet. Here, we investigated the effect of chronic alcohol consumption on the phenotypic change in BM macrophages.

Method: Wild type and GREAT (IFN-γ reporter) mice or mice with natural killer (NK) cell-specific Grm5 depletion were fed with liquid ethanol (EtOH) or isocaloric (Pair) diet for 8 weeks. The phenotypic changes of immune cells in BM were assessed by flow cytometry. In vitro, BM stromal cells (BMSCs), BM NK cells and BM macrophages were treated with ethanol, glutamate or IFN-γ. Moreover, glutamate production was examined by HPLC. In addition, western blotting, immunostaining, and qRT-PCR analysis were performed.
Results: As results of immunostaining, the expression of alcohol dehydrogenase 1 (ADH1) was significantly increased in BMSC around capillaries of EtOH-fed mice compared to Pair-fed controls. In parallel, high expression of *Adh1* and *Aldh2* mRNAs was observed in LepR$^+$ BMSCs by analyzing the public data base of single cell sequencing in mouse BM. *In vitro,* ethanol treatment increased the expression of *Adh1* mRNA and glutamate excretion in BMSCs through xCT transporter. Interestingly, IFN-γ production was specifically increased in BM NK cells near ADH1-expression BMSCs in EtOH-fed mice compared to those of Pair-fed mice. However, IFN-γ production was significantly decreased by depletion of metabotropic glutamate receptor 5 (mGluR5) in NK cells. In addition, IFN-γ treatment elevated the expression of pro-inflammatory mediators such as *Il1b, Il6,* and *Tlr4* mRNAs, whereas it decreased the mRNA expression of CX3C chemokine receptor 1 (*Cx3cr1*) in F4/80$^+$CD11b$^+$ BM cells.
Conclusion: Chronic alcohol consumption induced xCT-mediated excretion of glutamate in BMSCs, and released glutamate stimulated mGluR5-expressing BM NK cells to produce IFN-γ for the polarization of BM F4/80+CD11b+ cells into pro-inflammatory cells. Consequently, primed BM F4/80$^+$CD11b$^+$ cells by alcohol metabolism could migrate into the liver and aggravate alcoholic liver injury.

THU107

Epigenetic basis of monocyte dysfunction in severe alcoholic hepatitis

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Background and Aims: Severe forms of alcohol-related liver disease are associated with increased susceptibility to infections contributing largely to their poor prognosis. The cellular and molecular mechanisms responsible for this altered host defense are incompletely understood. We explored phenotypic profiles of the main subsets of the mononuclear phagocyte system (composed of monocytes and dendritic cells [DCs]) in ALD.
Method: We performed whole blood phenotypic analysis and ex vivo stimulation with various pathogen-associated molecular patterns (PAMPs) in 34 patients with alcohol-related cirrhosis (18 of which had biopsy-proven severe alcoholic hepatitis [sAH]), 12 healthy controls and 11 patients with chronic alcohol consumption without significant liver disease. We also evaluated the transcriptomic (RNA-seq) and chromatin accessibility (ATAC-seq) profiles of sorted CD14$^+$ monocytes from a subset of patients.
Results: Circulating monocytes and cDCs from patients with sAH displayed complex alterations characterized by increase of activation and inhibitory surface markers and impaired pro-inflammatory response, particularly in the IL-12p70/IFNγ/CXCL10 axis, upon stimulation with PAMPs representative of gram-negative bacteria (LPS, Pam3CSK4) or fungal pathogens (Zymosan). Their decreased ability to produce more than one cytokine (polyfunctionality) upon PAMPs stimulation was correlated with the risk of developing infection at 28 days and mortality at 90 days (Figure). Moreover, sorted CD14$^+$ monocytes of patients with sAH displayed altered transcriptional profile characterized by downregulation of genes related to key immune pathways such as innate immune responses, cytokines, response to IFNs and antigenic presentation and dysregulation of genes of metabolic pathways such as lipid metabolism, cellular respiration and translation. This profile displays striking similarities with monocytes from patients that recovered from sepsis or exposed to IL-10. Moreover, we observed extensive modifications in the chromatin accessibility, mainly in the enhancer regions with increase for AP1 (Jun/Fos), CEBP and MAF binding sites and decrease of NF-kB, STATs or IRFs motifs, in the monocytes from sAH patients. Based on the binding and expression target analysis package, regulatory regions that were more or less accessible were clearly associated with genes that were up or down-regulated in monocytes from sAH, respectively.
Conclusion: The altered transcriptional program and functional properties of monocytes from sAH patients contributing to their susceptibility to infection have strong epigenetic determinants.

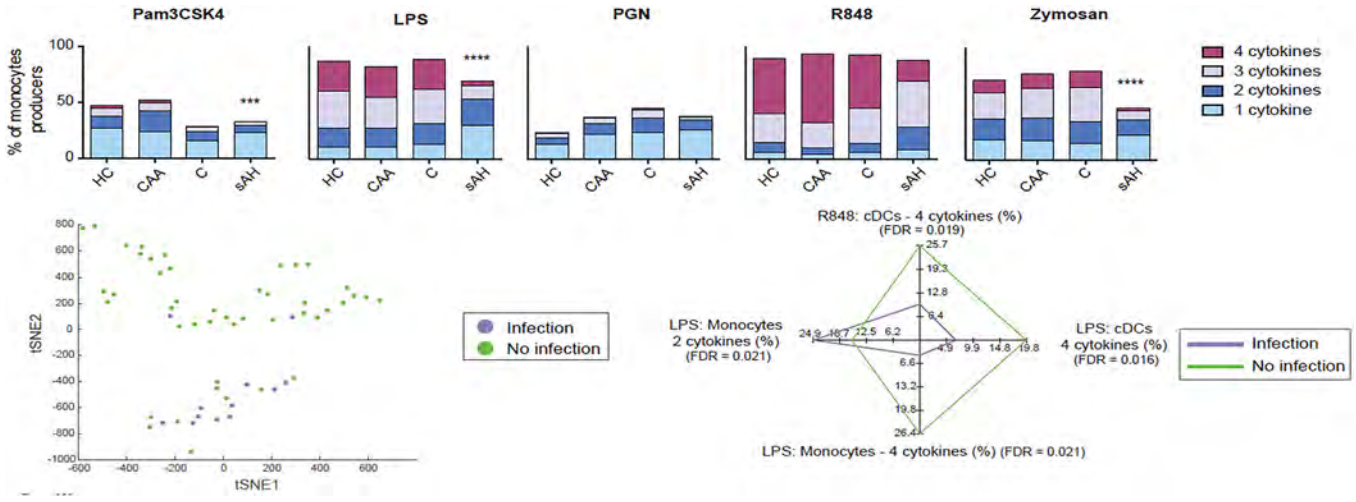

Figure: (abstract: THU107)

THU108

Plasma protein glycomics combined with circulating fragments of cytokeratin-18 are reliable biomarkers to diagnose alcoholic hepatitis

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Background and Aims: Alcoholic hepatitis (AH) is a severe liver disease with high mortality if left untreated. The hallmark of AH diagnosis remains histologic examination of a liver biopsy specimen. Transjugular liver biopsy being not available in all centers, there is a need for non-invasive biomarkers of AH. We recently showed that circulating fragments of cytokeratin-18, called M65, are higher in patients with HA and identified cut-off values. The goal of this study was to assess plasma N-glycomic profile of patients with HA and determine whether this glycomic profile could allow non-invasive diagnosis of HA in patients with clinical suspicion of this disease.
Method: Plasma N-glycomic profiles were analysed using DNA sequencer assisted fluorophore assisted carbohydrate electrophoresis (DSA-FACE). This analysis was performed on plasma samples from a prospective cohort of patients with a clinical suspicion of AH (n = 87) who underwent a transjugular liver biopsy. An optimal glycomic profile related to the diagnosis of AH was defined using logistic regression.
Results: Out of the 87 patients included (82% male, median age 53), 44 patients had biopsy proven AH. Patients with AH had a different plasma protein glycosylation profile from patients without AH, characterized by increase in branch fucosylated triantennary glycan (NA3Fb), known to be related to acute phase response, and decrease of undergalactosylated glycans (NG1A2FB). A combination of these glycans (log NA3Fb/NG1A2F) was higher in patients with AH than in those without (OR 3.9 (p = 0.001; 95% CI 1.8–8.8)) (Fig. A). Using –1.0 and –0.4 as thresholds for this combination of glycans to exclude and diagnose HA respectively, liver biopsy could be avoided in 69% of the patients and 75% were correctly classified. When restricting the analyses to the 63 patients with a suspicion of severe AH (age, bilirubin, INR, and creatinine (ABIC) score B or C), using the same cut-offs, liver biopsy could be avoided in 65% of patients with a diagnostic accuracy of 81%. Combining the glycomic marker with plasma M65 levels further increased diagnostic accuracy for AH to 97% and could avoid liver biopsy in 55% of patients with ABIC score B or C (Fig. B and C).
Conclusion: A specific plasma glycomic signature (log NA3Fb/NG1A2F) is strongly associated with the presence of biopsy proven AH in patients with a clinical suspicion of this disease. Combining this glycomic signature with plasma M65 concentration in patients with a suspicion of severe AH can avoid liver biopsy in 55% of the patients, with a high diagnostic accuracy of 97%. These markers

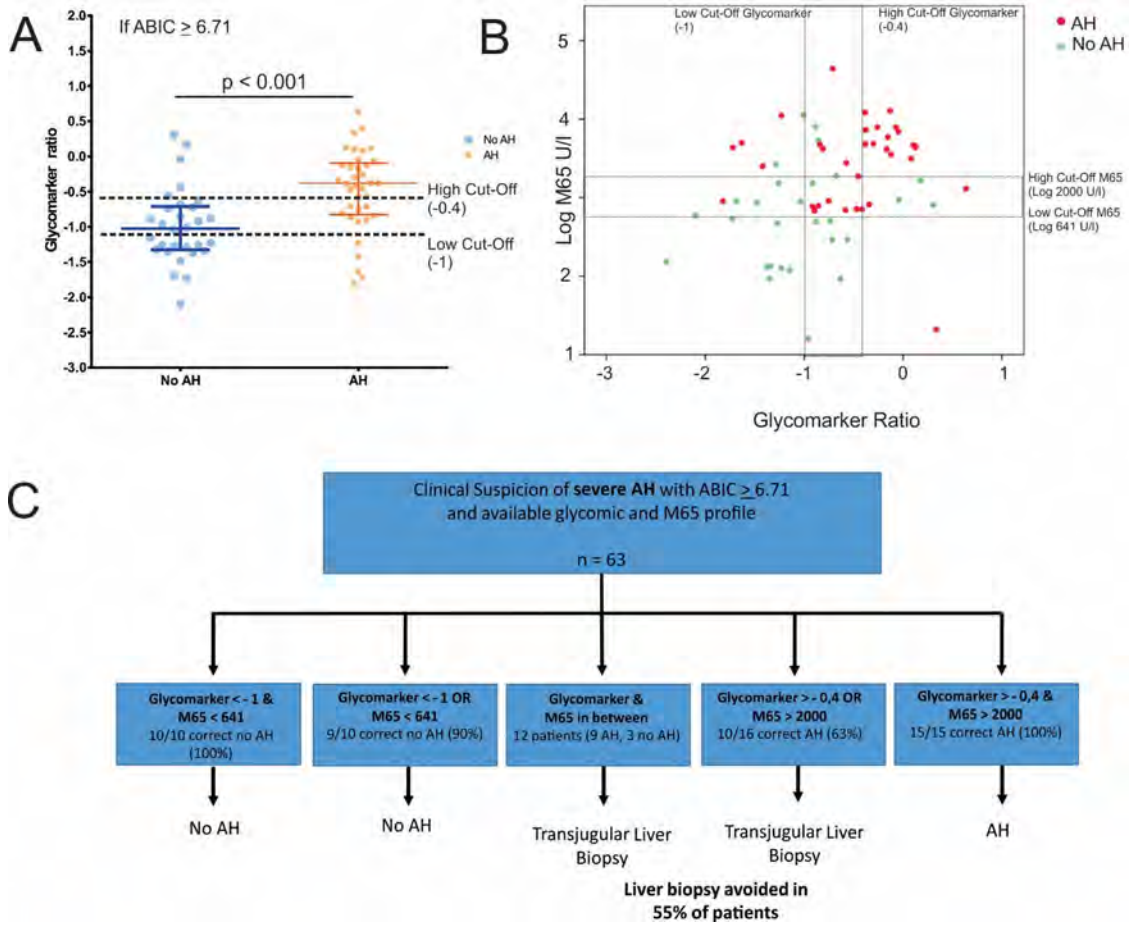

Figure: (abstract: THU108)

can be analysed using routine equipment, facilitating clinical implementation.

THU109

Role of NOX1 on hepcidin signaling in the crosstalk between macrophages and hepatocytes

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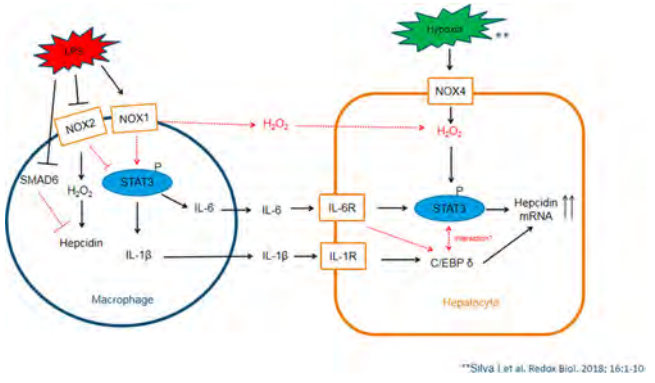
Background and Aims: Liver-secreted hepcidin is the systemic master switch of iron homeostasis and its dysregulation leads to iron accumulation in most of chronic liver diseases. Hepcidin is regulated by iron, inflammation or H_2O_2, but the role of NOX1 and its products ROS/H_2O_2 in monocyte-derived macrophages on hepcidin regulation under (patho)physiological conditions is poorly understood. We here investigate the role of NOX1 on regulating hepcidin and cytokines in inflammatory macrophages and subsequent effects on hepatocytes mimicking (patho)physiological conditions (cell ratios, oxygen levels and inflammation).
Method: THP-1 monocytes were differentiated into macrophages and co-cultured with Huh7 cells at (patho)physiological cell ratios (4:1) and treated with different LPS concentrations (10 ng/ml and 100 ng/ml) under normoxia (21% O_2) or hypoxia (1% O_2). The exposure of Huh7 cells to macrophage-conditioned medium with LPS was also investigated. Hepcidin, IL-1β, IL-6, C/EBPδ and SMAD6 mRNA levels were assessed by qRT-PCR and the expression of NOX1, p-STAT3, STAT3 and p-SMAD1/5/8 proteins were analyzed by western blot.
Results: LPS significantly increased NOX1, p-STAT3, IL-1βand IL-6 levels in THP-1 macrophages, but decreased STAT3 expression in a concentration-dependent manner under 21% and 1% O_2. Interestingly, 10 ng/ml LPS increased the expression of hepcidin whereas 100 ng/ml LPS decreased the expression of hepcidin under 21% O_2. In contrast, both LPS concentrations decreased the expression of hepcidin 1% O_2 in THP-1 macrophages. In addition, LPS decreased SMAD6, p-SMAD1/5/8 and CEBPδin THP-1 macrophages under 21% O_2. Notably, treatment of Huh7 cells with LPS had no effect on the expression of IL-6, IL-1β, CEBPδ and hepcidin in Huh7 cells under 21% O_2. Using inflammatory macrophage/hepatocyte co-cultures with direct cell-cell interactions under 21% O_2 increased IL-6, IL-1β, CEBPδ and hepcidin expression level in a concentration-dependent manner but did not further increase hepcidin in direct macrophage/hepatocyte co-cultures under 1% O2.



Conclusion: Our findings underscore a possible role of NOX1 and subsequent ROS/H_2O_2 concentrations on hepcidin regulation and induction of cytokine production in inflammatory macrophages involving the STAT3 signaling pathway. In the future, we aim at studying in detail hepcidin signaling by using WT and truncated hepcidin promoter constructs and siRNA-mediated knockdown of TLR4, NOX1, STAT3 or C/EBPδ.

Autoimmune and chronic cholestatic liver disease: Experimental and pathophysiology

THU110

Single-cell analysis of self-antigen-specific CD4 T cells reveals the B helper signature and the peripheral reservoir of autoreactive T cells in autoimmune hepatitis

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Background and Aims: In autoimmune disorders, CD4 T cell-dependent chronic B cell activation towards multiple self-antigens promotes the production of pathogenic auto-antibodies. In autoimmune hepatitis (AIH), the presence of anti-Soluble Liver Antigen (SLA or SepSecs) autoantibodies is associated with significantly reduced overall survival. However, the molecular signature and precise phenotype of autoreactive CD4 T cells in human autoimmunity have been elusive, even more so for rare diseases like AIH.
Method: Here, we combined brief *ex vivo* restimulation with pools of overlapping antigen-derived peptides and integrative single-cell RNAseq (scRNAseq) to characterize the circulating CD4 T cell response against Soluble Liver Antigen (SLA or SepSecs) in seropositive (defined as positive for anti-SLA auto-antibodies) and seronegative AIH patients.
Results: Only seropositive AIH patients had detectable amounts of SLA-specific CD4 T cells, which had a conserved memory CXCR5^{neg} PD-1^{high} CCR6^{neg} phenotype. Single-cell RNA-seq revealed their pro-inflammatory/B-Helper profile with high expression of *IL21, IFNG, TIGIT* and *CTLA4*, but also *NR3C1, CD109, KLRB1* and *CLEC2D*, among other genes. Strikingly, the expanded SLA-specific CD4 TCR clonotypes identified by scRNAseq were only found in the circulating CXCR5^{neg} PD-1^{high} CD4 T cell population, which was significantly increased in the blood of AIH patients and shared B helper capacity with the classical CXCR5^{high} PD-1^{high} CD4 T_{FH} population. Finally, we identified a specific phenotype (PD-1+CD38+CD27+CD127-CXCR5-) of T cells linked to disease activity during AIH.
Conclusion: Altogether, our results provide for the first time a fine and comprehensive characterization of autoreactive CD4 T cells in the rare autoimmune disorder AIH, thereby identifying the phenotypic niche and specific molecular signature of pathogenic B helper self-reactive CD4 T cells. The transcriptomic and phenotypic analysis presented in this study will be instrumental to track autoreactive CD4 T cells in other immune disorders and to design new therapeutic strategy.

THU111

FXR agonists repress innate and adaptive effector cytokine production in primary sclerosing cholangitis

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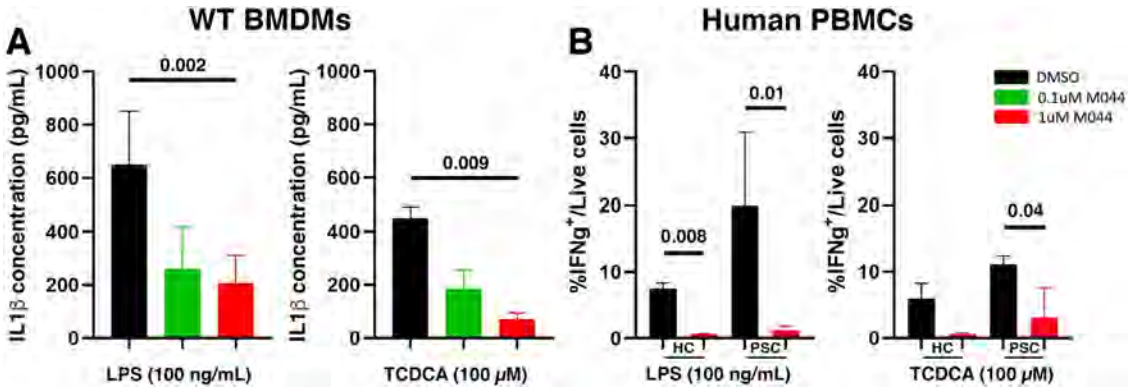

Figure: (abstract: THU111)

Background and Aims: While the etiology of primary sclerosing cholangitis (PSC) remains unknown, toxic bile induced injury to cholangiocytes and sterile inflammation likely contribute to the progressive destruction of bile ducts and fibrosis in this autoimmune liver disease. Farnesoid X receptor (FXR) agonists were recently found to improve biomarkers of biliary injury in clinical trials in PSC. Here we aim to delineate the mechanism of action by which FXR agonists attenuate liver inflammation in PSC.
Method: Transgenic mice lacking FXR expression in myeloid cells (FXRΔMP) were generated from Fxrfl/fl and LysM Cre mice. 45-day-old female FXRΔMP (and wild type) were fed 0.1% DDC diet for 7 days to induce cholangiopathy and liver inflammation. Bone marrow derived macrophages (BMDM)s from WT and FXR–/– mice were stimulated with either 100 ng/mL of LPS or 100uM of the hydrophobic bile acid Taurochenodeoxycholic acid (TCDCA) in presence of 0.1 or 1.0 uM of M044, an FXR agonist (or vehicle DMSO) before supernatants were assayed for IL1b using a TR-FRET assay. Peripheral blood mononuclear cells (PBMCs) from healthy controls (HC; n = 2) and from PSC patients (n = 4) were cultured under similar conditions and IFNg- and TNFa-productions were measured by qPCR and flow cytometry.
Results: DDC challenge resulted in higher plasma ALT levels in FXRΔMP compared with wt mice (mean 4140 vs 2340 IU/L, $p < 0.05$). Gene expressions for IL1b, TNFa, and IL6 were increased by 5, 4 and 3-fold, respectively, in hepatic mononuclear cells from FXRΔMP vs wt mice ($p < 0.05$). LPS and TCDCA induced IL1b expression in BMDMs (Fig. 1A). Pretreatment with the FXR agonist M044 dose-dependently reduced IL1b production in wt BMDM, but not in those from FXR–/– mice. Gene expressions for IL1b, NLRP3 and TNFa were increased in freshly isolated PBMC from PSC patients compared with HC, and decreased upon short term cultured with M044. LPS and TCDCA stimulation induced IFNg production in PBMCs from PSC patients, less so from HC, which reduced upon FXR agonist treatment (Fig. 1B). More than 45% of the cellular producers of IFNg in PBMCs from PSC patients resided in the CD4+ or CD8+ lymphocyte compartment.
Conclusion: Hydrophobic bile acids directly induce IL1b production by macrophages. FXR agonists repress these innate macrophages responses which diminishes their capacity for licensing effector cytokine production by CD4 and CD8 lymphocytes. Collectively, our data suggest that the mechanisms of action of FXR agonists in the treatment of PSC includes both the reduction of bile acid de-novo synthesis and suppression of innate and adaptive immune cytokine responses.

THU113

Absence of BSEP (ABCB11) protects MDR2 (ABCB4) KO mice from cholestatic liver and bile duct injury through modulating hepatic and intestinal inflammatory signaling

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Email: michael.trauner@meduniwien.ac.at.

Background and Aims: Metabolic preconditioning with a hydrophilic bile acid (BA) pool protects Bsep KO mice from acquired cholestasis. We aimed to explore whether increased BA detoxification alters inflammatory signaling, thereby improving liver injury in the Mdr2 KO mouse.
Method: Cholestatic liver injury was studied in Mdr2/Bsep DKO and Mdr2 KO mice. BDL WT and Mdr2 KO mice were treated with tetrahydroxylated BA (THBA). Gene expression profile of inflammatory/fibrotic markers was investigated. Immune cell profiling from liver was done by FACS. Cytokine ELISA and microbiota analysis were also performed. Impact of THBA on CDCA induced inflammation in IHH cells and RORgt as well as NFkB signaling in Jurcat cells (GFP-NFkB) were analyzed. Impact of THBA on CDCA induced gut permeability was studied in intestinal organoids.
Results: In contrast to Mdr2 KO, DKO mice displayed increased BA hydroxylation and lack of features of sclerosing cholangitis (hepatic and intestinal inflammation, fibrosis, ductular proliferation). 67% of serum BAs in DKO mice were polyhydroxylated (THBAs most prominent), while Mdr2 KO mice had no such BAs. THBA feeding reduced inflammation (IL1b, Cxcl1 by 50%) and fibrosis (Col1a2 by 80%) in Mdr2 KO. In WT BDL mice, bile infarct size and inflammatory gene expression (F4/80 –50%, Cxcl1 –55% and Cxcl2 –75%; $p < 0,05$) were profoundly reduced by THBA. Increased levels of THBAs were associated with reduced RORgt+ (TH17 differentiation) but increased FOXP3+ (Treg differentiation) and GATA3+ (TH2 differentiation) cell in the hepatic CD4+CD3+ T cell pool. Accordingly, serum levels of anti-inflammatory cytokine IL10 (related to TH2 cells), was increased in DKO as well as in THBA fed Mdr2 KO and BDL mice. Also, microbiome composition differs between Mdr2 KO and DKO animals. In vitro,

THBA treatment improved CDCA induced gut permeability in intestinal organoids (eCadherin IHC). In IHH cells, THBA reduced CDCA induced inflammation (mRNA IL8, Icam, Cxcl2; p < 0,05) and attenuated CDCA-induced NFkB activation in GFP-NFkB Jurcat cells. Also in Jurcat cells, THBA attenuated RORgt signaling at mRNA levels (IL23–55%, TGFb-25%; TH17 related cytokines).
Conclusion: Increased formation of THBA (due to absence of Bsep) or THBA administration represses key pro-inflammatory signals such as NFkB and RORgt in hepatocytes and immune cells and reduces intestinal gut permeability, thereby protecting Mdr2 KO mice from cholestasis-associated inflammation and fibrosis.

THU114
Predicted risk of end stage liver disease utilizing the UK-PBC risk score with continued standard of care and subsequent addition of obeticholic acid for 60 months in patients with primary biliary cholangitis

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Background and Aims: The UK-PBC Study group developed and validated a long-term prognostic model of primary biliary cholangitis (PBC) based on data collected from over 3000 patients with PBC. The model identified baseline albumin and platelets, in addition to ALT or AST, ALP, and total bilirubin, as independent predictors of risk of end-stage liver disease (ESLD; liver-related death or liver transplant) following 12 months of treatment. POISE was a randomized double-blind (DB), placebo-controlled 12 month Phase 3 trial investigating daily 5 mg to 10 mg obeticholic acid (OCA) for the treatment of PBC. Upon completion of the DB phase, 97% of patients enrolled in an open label extension (OLE) wherein all patients received OCA. The purpose of this analysis is to assess the change in predicted risk of ESLD with the UK-PBC model in patients who had received placebo during the DB phase and then transitioned to OCA during the OLE.
Method: POISE inclusion criteria: PBC diagnosis, ALP ≥ 1.67x ULN and/or total bilirubin >ULN to <2x ULN, stable UDCA dose or unable to tolerate UDCA. 73 patients were randomized to the placebo arm of the POISE trial, 66 of whom enrolled in the OLE. Baseline, month 12 of the DB phase and OLE phase data through 60 months of OCA treatment were included in the UK-PBC algorithm to assess change in predicted risk of ESLD at 5, 10, and 15 years after 12 months of placebo and through the duration of OCA treatment in the same patient population.
Results: At baseline the placebo group was median (IQR) 55 (14) years old, 93% female, 90% white, and 93% received daily UDCA at a median (IQR) dose of 15 (4) mg/kg. After 1 year of continued standard-of-care treatment, placebo patients demonstrated a slight increase in predicted risk of ESLD (Table), due to worsening liver biochemistry. However, after 1 year of OCA treatment, predicted risk of ESLD at 5, 10 and 15 years was reduced to below baseline levels. Furthermore, through the 60 month duration of the OLE the median risk of ESLD was sustained below baseline levels.
Conclusion: In POISE, the UK-PBC risk score predicted a trend for increased risk of ESLD in patients with PBC treated with placebo for 12 months in addition to standard of care. Addition of OCA led to sustained improvements in serum biochemistry and reductions in predicted risk of ESLD for up to 60 months of OCA treatment.

Table. Predicted Risk of ESLD in Patients with PBC Before and After OCA Treatment[1]

Median (IQR)	Baseline (n=73)	DB Month 12 (n=68)	OLE Month 12 (n=58)	OLE Month 36 (n=48)	OLE Month 60 (n=24)
5-Year Risk (%)	1.9 (1.1, 3.5)	2.3 (1.1, 4.4)	1.4 (0.8, 3.3)*	1.3 (0.7, 2.1)*	1.6 (1.0, 2.7)*
10-Year Risk (%)	6.4 (3.8, 11.3)	7.5 (3.6, 14.0)	4.7 (2.7, 10.6)*	4.4 (2.5, 6.9)*	5.2 (3.3, 8.7)*
15-Year Risk (%)	11.5 (6.9, 19.9)	13.5 (6.6, 24.4)	8.5 (5.0, 18.8)*	8.0 (4.5, 12.5)*	9.4 (6.0, 15.7)*

[1] Patients received Placebo ± UDCA for 12 months during the double-blind phase, then OCA ± UDCA throughout the OLE.
*p<0.05. P-value for within group comparison using Wilcoxon Signed Rank test comparing Month 12 DB and Month 12, 36, or 60 OLE

Figure: (abstract: THU114)

THU115
Cell specific transcriptomic analysis reveals a disassociation between treatment response and peripheral markers of immune activation in primary biliary cholangitis

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Background and Aims: Primary biliary cholangitis (PBC) is an autoimmune liver disease. The first line therapy for PBC is UDCA; however, ~30% of patients do not respond (high-risk patients). Herein, we studied the transcriptomic profile of innate and adaptive immune cells in low and high-risk patients in order to understand whether differential gene expression could reveal biomarkers for more precise risk and treatment stratification of PBC patients.
Method: 47 patient samples (93.6% female) across 6 UK-PBC Research Centres were analysed; 16 high-risk (ALP >3 × ULN on treatment with UDCA, mean ALP = 481), 16 low-risk (ALP < 1.5 × ULN, mean ALP = 116.9) and 15 matched controls. The following immune cell subsets were sorted from peripheral blood mononuclear cells: 1) $CD19^+$ B cells, 2) $CD4^+CD25^{high}CD127^{low}$ Treg cells, 3) $CD4^+CCR6^+CXCR3^-$ Th17 cells, 4) $CD4^+CCR6^-CXCR3^+$ Th1 cells and 5) $CD14^+$ monocytes. RNA was extracted (mean integrity = 8.41) and sequenced on Illumina HiSeq2500 or HiSeq4000. RNA sequencing alignment and statistical analysis was completed with STAR and DESeq2 packages respectively. Weighted Gene Co-expression Network Analysis was used to construct gene co-expression networks.
Results: In case-controls analysis, in Th1 cells, we identified gene co-expression networks with eigengene correlated with disease status (Pearson's correlation coefficient [PCC] = 0.59, p = 0.0005) that were enriched for pathways of regulation of NFκB induction, cell death, TNF pathway, JAK-STAT signalling, all supportive of a high Th1 immune cell activation. In Th17 cells, we identified co-expression networks with eigengene correlated with disease status (PCC = 0.47, p = 0.008), enriched for IL-17, TNF and NFκB signalling pathways and Th17 cell

differentiation, supportive of Th17 cell activation. Some overlap with previously identified pathways from GWAS studies was also identified (e.g. *TNFAIP3, IRF8, SPIB).* In CD14 cells, we found no clear pathway enrichment, suggesting that other cell types might be involved in innate hypersensitivity observed in PBC. In within-case analysis (i.e. high versus low-risk patients), no clear informative pathway enrichment was shown in any cell type, suggesting that stratification by risk of disease progression, based on ALP, does not identify any distinct transcriptomic signals.

Conclusions: Cell specific transcriptomic analysis, using peripheral blood, in patients with PBC revealed regulatory pathways relevant to disease biology. Regardless of treatment stratification based on biochemical response to UDCA the immune pathways seemed to remain activated. Overall, TNF, IFNγ and JAK-STAT signalling pathways appear to be activated and thus biologically important in patients with PBC.

THU116

Distinct intrahepatic molecular signature between relapse and sustained remission of autoimmune hepatitis before initiation of immunosuppression withdrawal

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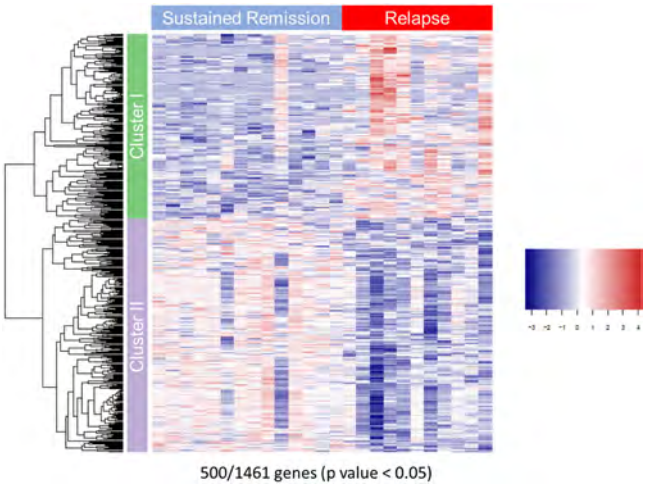
Background and Aims: The majority of autoimmune hepatitis (AIH) patients reach biochemical remission (BR) under steroid and azathioprine based therapies. After at least 2 years of BR an immunosuppression withdrawal can be attempted, although a relapse is common even when histological remission of AIH is achieved. So far, immunosuppression withdrawal is done in an "trial and error" manner in the absence of validated prediction factors beyond the achievement of histological remission.

Method: 29 patients with AIH under ongoing immunosuppressive therapy with biopsy proven histological remission (HAI<4) with subsequent complete withdrawal of immunosuppressants were recruited at two centers (Hannover: n = 22; Hamburg: n = 7). Intrahepatic gene expression was analyzed via mRNA sequencing from pre-weaning liver biopsies. Additionally, intrahepatic T cell compartment including regulatory T cells (Treg) was analyzed in immune histology.

Results: Immunosuppression was withdrawn after in median 72 (range: 27–170) months of therapy and after 53 (7–128) months of documented biochemical remission. AIH relapsed in 15/29 (52%) of patients after 11 (0.5–67) months.

When baseline laboratory characteristics before initiation of weaning were compared, patients with subsequent relapse had lower ALP (p = 0.011; AUC = 0.789), higher bilirubin levels (p = 0.017; AUC = 0.766), both within the normal range, and higher mHAI (p = .037; AUC = 0.766). Liver infiltration with T cell ($CD4^+$ and $CD8^+$) and $CD4^+FOXP3^+$ regulatory T cells was not significantly different between patients with and without relapse.

In the transcriptome sequencing of pre-weaning liver biopsies 1461 transcripts were differentially expressed (adjusted p-value < 0.05) between patients with and without AIH relapse (Figure). Interestingly, most significantly regulated genes were not related to obvious immune functions. Area under the curve of significantly regulated genes to predict relapse ranged from 0.545–0.944 with 11 genes with an AUC>0.900. Pathway analysis and further generation of a predictive molecular biomarker is matter of ongoing work.



Conclusion: Clinical routine and histological parameters seem inferior to intrahepatic gene expression analysis to predict relapse after immunosuppressant withdrawal. The molecular phenotype of baseline liver biopsies before immunosuppression withdrawal promise a better diagnostic tool for personalized medical approaches in the future than currently used clinical routine parameters.

THU117

Metagenomic sequencing in primary sclerosing cholangitis highlights microbial metabolism of essential nutrients and multiple altered species

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Background and Aims: While the composition of the gut microbiome in primary sclerosing cholangitis (PSC) is known to differ from healthy controls (HC), it would be of major importance to delineate functional microbiome changes which could influence the host and disease phenotype. We therefore performed, to our knowledge, the first shotgun sequencing study to characterize the genetic potential of the gut microbiome in PSC as compared with HC and patients with inflammatory bowel disease (IBD) but without liver disease.

Method: Fecal DNA from 2 cohorts from Norway and Germany (in total PSC n = 141 (n = 80 (56.7%) with concomitant IBD), HC n = 158, IBD without PSC n = 93) were subjected to metagenomic shotgun sequencing, generating ~15 billion paired end sequences. Abundance of bacterial species, enzymes and metabolic pathways (MetaCyc) were calculated using the HUMAnN2 and MetaPhlAn2 pipelines, and analysed using generalized linear models and a random effects meta-analysis (Q_{fdr} <0.05, unless otherwise stated).
Results: PSC patients had markedly fewer microbial genes compared to HC (p < 0.001), but borderline more genes than IBD patients (p = 0.05). Compared to HC, PSC patients showed enrichment of several *Clostridium* and *Veillonella* species, and a depletion of e.g. *Eubacterium spp., Barnesiella intestinihominis* and *Ruminococcus obeum. Klebsiella pneumoniae* was only detected in 24% of the PSC patients but at higher frequency than HC (4%, p < 0.001). Comparing PSC to IBD there was a significant increase in the prevalence of *Ruminococcus spp.* Extensive differences were observed between PSC patients and controls when analysing microbial gene functions and metabolic pathways, including changes in biosynthesis of essential nutrients like branched-chain and aromatic acids, several B vitamins and chorismate. There were fewer genes related to chorismate biosynthesis in PSC vs HC, while higher levels were found in PSC with IBD compared to IBD. When directly comparing PSC patients with and without IBD there were no differences for any species or functions. Notably, there was increased abundance of genes related to e.g. ammonia production and antibiotic resistance in PSC compared to HC.
Conclusion: The gut microbiome in PSC exhibits large compositional and functional differences compared to HC, irrespective of the presence of IBD. The impact of these on the disease severity and progression should be investigated further to identify potential disease-modifying targets.

THU118
Obeticholic acid but not bezafibrate treatment improves cholestasis-induced cognitive decline

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Background and Aims: Primary Billiary Cholangitis (PBC) is a chronic cholestatic liver disease. PBC and other cholestatic patients experience cognitive symptoms, including problems with short-term memory and concentration, associated with central fatigue. This 'brain fog' has major indications for poor quality of life in patients, partly because it is not improved by currently licensed therapy. Recent trial data have suggested that the PPAR-α agonist Bezafibrate is effective at improving liver injury markers in PBC patients needing 2nd line therapy.
The aim of this study was to utilise the Bile Duct Ligation (BDL) model to explore the potential therapeutic benefit of Bezafibrate, with emphasis on cognitive symptoms. We compared BZ with approved 2nd line therapy - FXR signalling anti-cholestatic agent Obeticholic Acid (OCA).
Method: C57BL/6 mice underwent BDL surgery. Sub-groups of BDL were treated with either Bezafibrate (n = 7), or OCA (n = 9), or left untreated (n = 16). Spatial memory and cognitive function were evaluated by standardised behavioural tests. Animals were harvested at day 10 with liver and brain taken for histology.
Results: Liver fibrogenesis (αSMA+ myofibroblasts and Picrosirius Red) was significantly reduced in both Bezafibrate and OCA treated mice when compared to BDL (Table 1).

Table 1

	BDL	OCA	Bezafibrate
PSR	4.8%	**1.8% (⇩−62%)** ***	**1.4% (⇩−70 %)** ***
αSMA	4.12%	**2.3% (⇩−45%)** **	**2.2% (⇩−47%)** **
P21	34.5	**7 (⇩−80%)** ***	75.8 (⇧+120%) ***
Time in Novel Arm	30.6%	**65% (⇧+111%)** **	35.27% (+15%)

p21+ cellular senescence in the liver is a known feature of cholestatic disease and associated with disease progression. p21+ senescent hepatocytes are elevated in BDL but significantly reduced with OCA therapy. Conversely, Bezafibrates treatment showed no reduction in cellular senescence (Table 1), and in fact led to more hepatocyte senescence in this model.
Spatial memory (as assessed by the Time in the Novel Arm in the Y-maze) was impaired in BDL mice but OCA therapy rescued the cognitive decline, leading to near normal cognitive ability. In contrast, Bezafibrate treatment had no beneficial effect on cognition and spatial memory in the BDL model.
Conclusion: We report that Bezafibrate limited liver fibrosis but failed to reduce liver cellular senescence and to improve cognitive function in BDL, even when used as an early intervention. Consistent with our previous studies, OCA therapy attenuates fibrogenesis and prevents cognitive symptoms in cholestatic BDL mice. Our data suggests that the cognitive effects of OCA are through a direct FXR-mediated effect rather than an indirect effect through reduced cholestasis.
Obeticholic acid but not Bezafibrate may provide an effective treatment for patients experiencing cognitive deficit, if used early in the disease process.

THU119
Negative immune regulator LNK/SH2B3 contributes to the development of autoimmune liver disease in mice under fatty-metabolic stress

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Background and Aims: In search for disease susceptible genes in autoimmune liver disease, GWAS study has identified a missense variant of Lnk/Sh2b3 (Lnk) as a risk of autoimmune hepatitis (AIH). We previously reported that Lnk gene is a negative regulator of immune cell activation through Janus kinase 2 and 3 signaling and plays an essential role in hematopoiesis. However, the causal relationship between Lnk gene and the pathogenesis and regulatory mechanism of liver autoimmunity is undisclosed. By using a Lnk knockout (KO) mice, we sought to test the hypothesis that metabolic stress to the liver could enhance the risk of autoimmune phenotypes in patients who possess relevant genetic predisposition.
Method: In order to clarify the impact of metabolic stress/lipid storage on the expression of Lnk/Sh2b3 gene, we examined the expression of Lnk in liver tissue or PBMC obtained from patients with NASH /NAFLD. Furthermore, Lnk deficient mice were loaded with normal diet (ND) or high fat and high cholesterol diet (HF/HCD) for 6 or 12 weeks and serum and liver tissues were analyzed.
Results: The expression of Lnk/Sh2b3 was significantly decreased in PBMC and liver tissue of NASH/NAFLD patients compared with healthy individuals. Lnk KO mice showed no sign of liver inflammation with ND. However, with HF/HCD feedings, AST and ALT levels and inflammatory cytokines were significantly elevated in Lnk KO mice. Moreover, significant increase of IgG and IgM and autoantibodies (anti-nuclear antibody, ANA) were observed in serum of Lnk KO mice. Histological analysis in the liver of Lnk KO HF/HCD mice showed that hepatic steatosis was aggravated and inflammatory foci around blood vessels was observed. However, interface hepatitis, typical findings of

AIH, was not observed. Analysis of intra-hepatic lymphocytes showed that CD8+ T cells, NK cells and CD19^{+} CD138^{+} plasmacytes were especially increased. Liver fibrosis was comparable at 12 weeks between wild type and Lnk KO mice fed with HF/HCD.
Conclusion: Lnk KO mice fed with HF/HCD mimic some aspects of disease entity of autoimmune traits combined with NAFLD/NASH. This mice model conveys the message that metabolic stress, or fatty liver disease, should be avoided in order to prevent the onset of autoimmune liver disease, especially those who have genetic predisposition.

THU120

Mast cell activation mediates biliary immunobiology and subsequent immune response in a model of primary biliary cholangitis

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Background and Aims: Primary biliary cholangitis (PBC) is characterized by biliary senescence, inflammation, and bridging fibrosis. Mutations in human leukocyte antigen (HLA, the major histocompatibility complex [MHC]) genes have been identified and may correspond with enhanced helper (CD4+) and cytotoxic (CD8+) T cell infiltration during PBC. Mast cells (MCs) infiltrate the liver during cholestasis, including PBC, and inhibition of MC activation reduces biliary senescence and liver fibrosis. MCs communicate with CD8+ T cells, macrophages and neutrophils in chronic liver disease; however, MC mediation of immune response during PBC has not been studied. We aimed to evaluate the role of MC activation in the promotion of immune responses during PBC.
Method: We used female wild-type (WT) and dnTGFβRII (at 34 wk of age, model of late stage PBC) mice treated with saline or cromolyn sodium (to block MC activation) for 1 wk by IP implanted osmotic minipump. MC presence was determined by staining for chymase and tryptase and activation was determined by serum tryptase and HA levels by EIA. Serum levels of antimitochondrial antibodies (AMA) were assessed by EIA. Liver inflammation was determined by immunostaining for MPO and F4/80. Biliary expression of MHC I (presents to CD4+ T cells) and MHC II (presents to CD8+ T cells) along with hepatic expression of CD4+ and CD8+ T cells was evaluated by immunostaining. Expression of IL-6 and TGF-β1 (pro-inflammatory for CD4+ T cells) and IL-4 and IFN-γ (increase cytotoxicity in CD8+ T cells) was determined by *q*PCR in total liver. Female human control and advanced stage (Stage III/IV) PBC samples were utilized and MC co-localization with CD4+ and CD8+ T cells was determined by immunostaining.
Results: dnTGFβRII mice had increased MC number/activation along with elevated serum AMA levels, which decreased following cromolyn treatment. Liver inflammation increased in dnTGFβRII mice but decreased after cromolyn treatment. Biliary expression of MHC I and II increased in dnTGFβRII mice, but was downregulated following cromolyn treatment. Changes in MHC expression corresponded with enhanced CD4+ and CD8+ T cell number, and increased expression of IL-6, TGF-β1, IL-4 and IFN-γ in dnTGFβRII mice, but these findings decreased in cromolyn treated mice. In humans with advanced stage PBC, increased portal MC presence corresponded with enhanced CD4+ and CD8+ T cells expression.
Conclusion: MC infiltration/activation is increased in advanced stage PBC and correlates with increased liver inflammation and immune response. Inhibition of MC activation reduces hepatic inflammation, biliary MHC expression and T cell infiltration. MCs may play a role in the autoimmune response noted in patients with PBC; therefore, inhibition of MC activation may be therapeutic for PBC patients.

THU121

MSCs attenuate cona-induced autoimmune hepatitis in mice through Nrf2/HO-1 pathway by altering macrophage polarization

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Background and Aims: The study found that Autologous transplantion of mesenchymal stem cells (MSCs) reduces concanavalin A (ConA)-induced Autoimmune hepatitis in mice. However, the mechanism of action of MSCs in ConA-induced Autoimmune hepatitis is still unclear.
Method: Zinc protoporphyrin (Znpp, the Ho-1 activity inhibitor) and Hemin (a HO-1 inducer) were injected into a mouse model of immunological Autoimmune hepatitis induced by ConA. The mice were sacrificed 12 hours after ConA injection. Blood samples and liver tissues were collected. The experimental animals were randomly divided into five groups: normal group, ConA group, ConA+MSCs group, ConA+MSCs+Znpp group and ConA+Hemin group; liver cell apoptosis was detected by TUNEL staining; liver cell proliferation was detected by Ki-67 immunohistochemical staining; The expressions of TNF-α, IFN-γ and IL-6 in serum were detected. The expressions of HO-1, Nrf2, INOS, Arg1, TNF-α, IFN-γ and IL-6 were detected by RT-PCR. The expression of HO-1 and Nrf2 in mice was detected by Western Blot; the expression of INOS and CD206 in mice was detected by immunofluorescence double staining.
Results: Compared with the ConA group and the Znpp group, the serum levels of ALT and AST in the MSCs group and the Hemin group were significantly lower(Fig 1). HE staining results showed that liver damage was improved in the MSCs group and Hemin group(Fig 2). The TUNEL immunofluorescence staining confirmed that the number of TUNEL positive cells in the MSCs group and the Hemin group was significantly lower than that in the ConA group and the Znpp group (Fig 3), while the number of Ki-67 positive cells in MSCs group and Hemin group was significantly higher than that in ConA group and Znpp group(Fig 4). The expression of TNF-α IFN-γ and IL-6 in conA group and Znpp group was higher than that in MSCs group and Hemin group(Fig 5). The RT-PCR assay also confirmed the difference

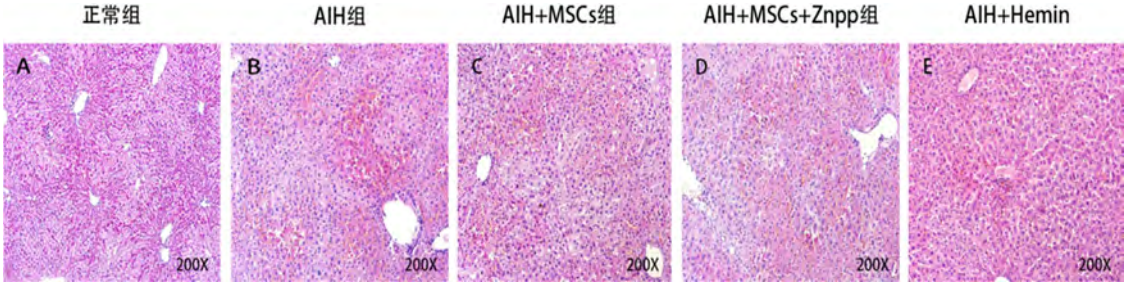

Figure: (abstract: THU121)

in expression of the above three inflammatory factors at the mRNA level(Fig 6). Western Blot assay showed high expression of HO-1 and Nrf2 in MSCs and Hemin groups(Fig 7). Immunofluorescence double staining showed that the expression of CD206 in MSCs group and Hemin group was significantly higher than that in ConA group and Znpp group, while the expression of INOS was significantly lower than that in ConA group and Znpp group(Fig 8). RT-PCR detection confirmed Arg1 in MSCs and Hemin group from mRNA level. High expression, and low expression of INOS in the MSCs and Hemin groups (Fig 8).
Conclusion: Our data demonstrate that MSCs attenuate ConA-induced Autoimmune hepatitis in mice, and the mechanism involves by altering macrophage polarization through Nrf2/HO-1 pathway.

THU122

Klebsiella in the mucosal gut microbiota in primary sclerosing cholangitis is associated with more severe disease

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Background and Aims: *Klebsiella pneumoniae* has been identified as a potential gut pathobiont in primary sclerosing cholangitis (PSC). Experimental evidence has suggested that the *K. pneumoniae* species is able to disrupt the epithelial barrier and elicit inflammation in the liver. We aimed to investigate the presence of *Klebsiella* in mucosal biopsies of PSC patients and its potential clinical impact.
Method: 184 consecutive PSC patients underwent ileocolonoscopy between 2006 and 2008. After excluding patients with previous colectomy or liver transplantation, we included 84 patients (79% inflammatory bowel disease [IBD], 77% male, median age 40 years and median 3.3 years disease duration) with biopsies available from at least two out of four segments (terminal ileum, ascending, descending and sigmoid colon). During a median observation time of 7.5 years, 52 patients (62%) were liver transplanted or died. DNA was extracted from biopsies and subjected to 16S rRNA amplicon sequencing (V3-V4) and analyzed using QIIME2. The dataset was rarefied to 9137 reads per sample.
Results: Sequences mapping to the *Klebsiella* genus in any segment were detected in 13 patients (15%). *Klebsiella* in any segment were associated with a higher mean Amsterdam-Oxford PSC risk score (AOM) (2.32 [1.86–2.78] vs. 1.94 [1.78–2.10], p = 0.037) and AST-to-platelet-ratio index (1.57 [0.94–2.21] vs. 1.00 [0.74–1.25], p = 0.009) compared to those without. There were no associations between *Klebsiella* and age, gender or IBD. Patients with *Klebsiella* in any segment had numerically shorter liver transplantation-free survival (median 4.2 vs. 8.7 years, p = 0.20, Kaplan-Meier analysis). Considering individual segments, *Klebsiella* in the sigmoid (n = 10/69, 14%) was associated with reduced survival (2.4 vs. 8.7 years, p = 0.026), but not independent from AOM risk score ($HR_{Klebsiella}$ 1.86 [0.88–3.90], p = 0.11, Cox regression). Other PSC-associated microbiota features like low diversity (Shannon) or increased *Veillonella* did not associate with survival, although, the group with microbiota diversity below median in the ascending colon had higher AOM score (p = 0.042) compared to those with above median.
Conclusion: The presence of *Klebsiella* in the gut mucosa is associated with more severe PSC. Further analyses are necessary to define abundance at species level. The possibility of targeting specific bacteria to modify the disease in subsets of PSC patients should be investigated further.

THU123

Downregulation of the bile acid receptor TGR5 in livers of PSC patients and ABCB4−/− mice

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Background and Aims: The localization of TGR5 in cholangiocytes and immune cells, the choleretic, anti-inflammatory and anti-apoptotic functions of the receptor suggest that TGR5 is important for the pathogenesis of liver diseases and in particular of biliary diseases. Aim of this study was to evaluate changes in TGR5 expression and localization in livers from PSC patients as well as from Abcb4$^{-/-}$ mice, which serve as an animal model for sclerosing cholangitis.
Method: TGR5 expression and localization in livers from PSC patients (cryopreserved IPSCIG cohort (n = 22) and paraffin embedded German cohort (n = 10)) and Abcb4$^{-/-}$ animals were evaluated using immunofluorescence staining and confocal laser scanning microscopy. TGR5 mRNA expression was analyzed in isolated intrahepatic and extrahepatic bile ducts from Abcb4$^{-/-}$ mice and WT controls by real-time PCR in relation to an endogenous housekeeping control. BECs (biliary epithelial cells) were isolated by microdissection and outgrow method or by FACS using positive selection for EpCAM from livers of 6–8 weeks-old animals. Biliary epithelium organoids were generated from human bile and liver biopsy samples. Human BECs were isolated from patients with alcoholic liver disease or non-alcoholic steatohepatitis. For Western-Blot analysis cell lysates were separated by SDS-page and blotted onto PVDF membranes. Detection was carried out using anti-TGR5, phospho-p44/42 MAPK, p44/42 MAPK and anti-GAPDH antibodies. The concentration of serum cytokine levels in Abcb4$^{-/-}$ and WT mice was determined using a Luminex cytometric bead assay.
Results: Reduced TGR5 staining intensity was detected in BECs from early and late stage liver tissue of PSC patients as well as in BECs of Abcb4$^{-/-}$ mice. Analysis of isolated intrahepatic and extrahepatic bile ducts showed a significant decrease in TGR5 mRNA in Abcb4$^{-/-}$ mice as compared to the respective controls. In addition, TGR5 mRNA levels were significantly lower in EpCAM^{+}-cells derived from Abcb4$^{-/-}$ animals. Stimulation of human biliary organoids and human BECs with recombinant IL-8 significantly supressed TGR5 mRNA expression and TGR5 protein levels, respectively. Moreover, the murine IL-8 homologues KC and MIP-2 were significantly increased in serum of Abcb4$^{-/-}$ mice compared to the WT controls and stimulation of isolated WT cholangiocytes with IL-8 homologues significantly decreased TGR5 mRNA in murine BECs.
Conclusion: The bile acid receptor TGR5 was significantly down-regulated in BECs of liver tissue from PSC patients with both early and late disease stages. Moreover, a significant reduction of TGR5 mRNA was detected in intrahepatic and extrahepatic bile ducts as well as in isolated BECs from Abcb4$^{-/-}$ mice livers. Our data demonstrate that IL-8 stimulation suppresses TGR5 mRNA and protein levels in murine and human BECs or biliary organoids.

THU124

Insufficient deletion of autoreactive CD4 T cells and plasticity of Tregs drive spontaneous autoimmune hepatitis in mice

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Background and Aims: Autoimmune hepatitis is a chronic inflammatory liver disease, which is associated with an adaptive immune response to hepatic antigens. We have previously described a new mouse model of autoimmune hepatitis, which is characterized by hepatocellular expression of an MHC class II-restricted CD4 T cell epitope of lymphocytic choriomeningitis virus (GP61–80) under control of the albumin promoter, and by abundance of cognate Smarta1 CD4 T cells recognizing GP61–80 (EASL Abstract in: Journal of Hepatology 2017; Vol.66, Issue 1, S74). By using these Alb-iGP_smarta mice, we elucidated some of the mechanisms that induce the loss of tolerance to liver antigens in experimental AIH.
Method: Autoreactive CD4 T cells and regulatory T cells in Alb-iGP_Smarta mice were identified with I-A(b) GP66–77 tetramers and analyzed by flow cytometry. Ectopic lymphoid structure formation in the liver was characterized by histological analysis of liver sections taken at various disease stages.
Results: Autoreactive T cells were not deleted in the thymus or in the periphery, due to antigen ignorance. Starting at 20 weeks of age, Alb-iGP_Smarta mice spontaneously developed CD4 T cell-mediated hepatitis with typical disease features of human AIH, including elevated IgG and serum transaminases, antinuclear autoantibodies, and lymphocytic periportal infiltrates with interface hepatitis. The development of AIH was facilitated by pathogenic maturation of autoreactive CD4 effector T cells towards IFN-γ and TNF-α co-producing cells, which seemed to occur locally in the liver within transiently formed portal ectopic lymphoid structures. Autoantigen-specific regulatory T cells in the liver displayed a selective increase of plasticity and instability, marked by IL-17 production, reduced Foxp3 expression and a less demethylated *Foxp3* locus, providing a possible explanation for their obvious inability to arrest the pathogenic maturation of CD4 effector T cells and AIH exacerbation.
Conclusion: Our findings indicate that AIH is driven by pathogenic maturation of previously ignorant autoreactive CD4 effector T cells, in combination with selectively increased

THU125

MIR-506 as one of potential determinants of different phenotypic presentation of ulcerative colitis in patients with primary sclerosing cholengitis (PSC)

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Background and Aims: Primary sclerosing cholangitis (PSC) is commonly accompanied by ulcerative colitis (UC), most frequently localized in the right colon. Impairment of $Cl^{-}/HCO3^{-}$ exchanger (AE2), promoted by release of Ca2+ *via* inositol-1,4,5-trisphosphate-receptor (InsP3R3), decreases luminal pH of the colon facilitating the entry of protonated toxic bile salts and sensitizing apoptotic stimuli. Non-coding miR-506 down-regulates AE2, InsP3R3, and also sphingosine kinase-1(SPHK1), the enzyme that activates sphingosine-1, a bioactive lipid involved in immune cell trafficking. We analyzed expressions of miR-506 and its target genes in colonic tissues of patients with PSC with concomitant UC (PSC-UC) and UC alone.
Method: Ascending and sigmoid colon biopsies were obtained from patients with PSC-UC (n = 11), UC (n = 8) and controls (n = 11). The relative levels of microRNAs and mRNAs were evaluated by real-time PCR. A potential effect of ursodeoxycholic acid (UDCA) was examined in Caco-2 cells.
Results: There was a significant increase in miR-506 level (6.7-fold, p = 0.0005 vs controls, and p = 0,0001 vs UC) in the ascending colon of PSC-UC patients. This was associated with downregulation of AE2 (43% reduction, p = 0.029 vs controls), with no changes seen in InsP3R3 and SPHK1 expressions. On the contrary, in the sigmoid colon of PSC-UC, miR-506 expression was substantially suppressed (60% reduction, p < 0.0001 vs controls) and accompanied by induction of SPHK1 mRNA (2.5-fold, p = 0.02 vs controls),while the other investigated factors remained unchanged. In reverse, expression of miR-506 in patients with UC was substantially suppressed both in the ascending and sigmoid colon (80% and 79% reduction, respectively) and the SPHK1 expression was noticeable enhanced (6.2-fold, and 3.8-fold, respectively). In contrast to PSC-UC group, the level of AE2 mRNA was enhanced (1.5-fold, p = 0.03 vs controls) in UC ascending colon, but InsP3R3 mRNA levels were comparable to control values in both parts of colon. UDCA did not affect the basal expression of miR-506.
Conclusion: A different phenotypic presentation of colitis in PSC may, at least partially, be related to miR-506 expression. In ascending colon of PSC-UC the upregulation of miR-506 may result in the failure of bicarbonate secretion, while in UC a downregulation of miR-506 may lead to enhanced production of sphingosine-1-phosphate that is involved in inflammatory responses.

THU126

Co-stimulatory molecules OX40 and CD30 mediates the regeneration of the liver epithelium in a mouse primary scletosing cholangitis model

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Background and Aims: Primary Sclerosing Cholangitis (PSC) is a chronic liver disease characterized by the accumulation of inflammation and fibrosis of the bile ducts. Efficient treatment for PSC is lacking due to the lack of understanding about the disease pathogenies. Regulatory T cells (Tregs) have been suggested to have important roles in PSC pathogenesis, and its regulation in the PSC microenvironment is less known. Tumor necrosis factor receptors OX40 and CD30 are T cell co-stimulatory molecules required for promoting T cell survival, effector phenotype and regulatory function. To investigate whether co-stimulatory molecules are required to facilitate the tissue regenerating potential of Tregs on the background of biliary injury, we utilised the OX40−/−CD30−/− double knockout (dKO) mice with the feeding of 3,5-diethoxycarbonyl-1,4-dyhydro-collidine (DDC) diet to induces cholestatic liver injury.
Method: dKO (n = 6) and wild type (WT) BL6 mice (n = 4) were fed with DDC diet for 7 days. Immune cells in the liver were isolated and liver histology were analyzed before and after injury.
Results: At homeostasis, WT mice have 4 times more Tregs in the liver compared to the dKO mice (4.1 ± 0.3% vs 1.1 ± 1.1%/CD4 + cells). Tregs in the dKO mice have impaired expansion following DDC diet compared to the WT group (7.4 ± 1.5% vs 2.3 ± 0.95% CD4+ cells). Further analysis demonstrated that liver sinusoidal endothelial cells are a major source of OX40 Ligand (OX40L) in the liver, and the level of OX40L expression significantly decreased after DDC diet (95 ± 0.2% vs 35.8 ± 3.7% /CD31 + cells). Histological findings showed that the dKO mice had significantly impaired hepatocyte regeneration

demonstrated by the increased in senescence marker p21 (58.9 ± 17.0 vs 24.7 ± 8.9 cells/field) and decreased proliferation marker Ki67 on Hnf4a+ hepatocytes compared to the WT mice (1.7 ± 1.1 vs 3.3 ± 1.6 cells/field) following injury, whilst no significant difference was detected at the homeostatic level.
Conclusion: Our results showed that costimulatory molecules OX40 and CD30 are able to regulate the degree of cellular senescence in response to injury, and suggest that this is controlled through a T-cell mediated manner in particularly through the regulation of Tregs.

THU127

Developing antigen-specific immunotherapy for autoimmune hepatitis type 2 by identification of T cell epitopes

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Background and Aims: Antigen-specific immunotherapy can modulate T-cell mediated immunological diseases by inducing tolerance. Autoimmune hepatitis type 2 (AIH2) is a severe autoimmune liver disease with unmet clinical needs, in which T-cells specific to autoantigen cytochrome P450 2D6 (CYP2D6) help perpetuate tissue damage. We aim to identify T-cell epitopes of CYP2D6 with tolerogenic potential, as a novel immunotherapy for AIH2 could offer an alternative to lifelong immunosuppression.
Methods: Paediatric and adult AIH2 patient (n = 16), adult AIH1 patient (n = 16) and healthy donor (n = 46) PBMC samples were screened for antigen-specific activation to 30mer peptides of CYP2D6 using ^{3}H-thymidine incorporation. Peptide-stimulated adult AIH2 samples were analysed for production of 13 T-cell cytokines. A flow based assay to enrich for rare antigen-specific CD4+ T-cells based on activation-induced markers (AIM+) and isolation by FACS prior to T-cell cloning is under development. HLA-DR transgenic mice (*HLA-DRB1*0401* and *DRB1*0301*) were immunised with CYP2D6 30mer peptides. Spleen and draining lymph node cells were stimulated *ex vivo* with 30mer peptide and overlapping 15mers. T-cell responses were assessed by proliferation, and IFN- γ and IL-2 ELISAs. T-cell hybridomas comprised of activated HLA-DR transgenic T lymphocytes and thymoma cell line BW5147 were generated for detailed epitope mapping. *HLA-DRB1*0701* transgenic mice for similar experiments are being re-derived.
Results: CYP2D6 is a highly immunogenic protein with Pep1, Pep2 and Pep4 recording frequent strong responses in AIH2 patients. Similar patterns are observed in healthy donors with the addition of responses to Pep9. Pep2 and Pep4 induce high levels of IL-6 production in adult patients. These peptides produce significant T-cell responses in HLA-DR4 and HLA-DR3 transgenic mice and T-cell hybridomas specific to these peptides recognise both the native CYP2D6 protein and overlapping 15mers.
Conclusions: Autoimmune Hepatitis Type 2, as a clinically challenging autoimmune liver disease, may benefit from the realisation of novel treatments. By combining approaches including interrogation of immune responses of AIH2 patients, AIH1 patients, healthy donors and humanised mouse models we can explore the immunogenicity and hierarchy of peptide epitopes in AIH2. Our aim, in progress, has been to identify T cell epitopes of CYP2D6 to develop a peptide cocktail for antigen-specific immunotherapy of AIH2.

THU128

Relevance of epidermal growth factor receptor kinase activity in a model of cholestatic liver injury

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Background and Aims: The epidermal growth factor receptor (EGFR) pathway is known to be an important player in both liver regeneration and hepatocarcinogenesis, but its role during cholestatic liver injury remains elusive and so it does its regulatory activity on adult hepatic progenitor cells (HPC) expansion and function in the cholestatic liver. Thus, the aim of this work is to analyze the effect of inhibiting EGFR signaling on the liver regenerative response and liver damage progression upon a cholestatic insult, with an eye on HPC.
Method: We have used a validated transgenic mouse model expressing a liver-specific truncated form of human EGFR which lacks its tyrosine kinase domain and acts as a dominant negative mutant (deltaEGFR). WT and deltaEGFR mice were submitted to 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC)-induced cholestatic liver damage for 1–6 weeks. Immunohistochemistry, immunofluorescence, western blot and RT-qPCR analyses were performed to characterize the gene/protein expression profile of inflammatory and fibrotic signals, HPC markers as well as to measure cell proliferation. Biochemical markers of liver damage were also measured in serum.
Results: Results show that lack of EGFR kinase activity leads to decreased liver damage and fibrosis upon DCC treatment, evidenced by lower serum biomarkers of liver injury (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and total bilirubin), and a lower induction of fibrosis markers. Interestingly, this is associated with a stronger ductular reaction and increased HPC expansion in response to DDC based on H&E staining, cytokeratin 19 immunohistochemistry, Ki67 immunofluorescence staining and HPC markers expression analysis. Additionally, profound changes in the expression profile of inflammatory mediators are observed in deltaEGFR mice, which suggest an altered inflammatory response. To clarify the EGFR-dependent mechanisms behind the altered liver regenerative response to DDC-induced cholestasis further experiments are being performed using an *in vitro* model of bile acid-induced cholestatic injury.
Conclusion: Collectively, our results reinforce the suitability of the deltaEGFR mouse model to allow us advance in our understanding on the mechanisms governing liver injury responses while supporting a major role for EGFR signaling pathway in regulation of liver regeneration and HPC behavior during chronic cholestatic liver injury. Ongoing mechanistic studies will help us elucidate the EGFR-dependent mechanisms underneath such role.

THU129

The role of cellular senescence in the natural course of primary sclerosing cholangitis

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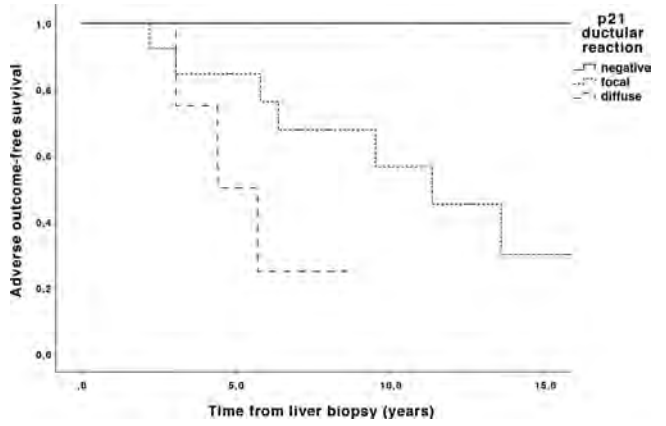
Background and Aims: Cellular senescence (CS) is a physiological mechanism of irreversible cell cycle arrest in response to damage, that prevents uncontrolled replication of injured cells. The role of CS in the pathogenesis of human chronic liver diseases has been recently reported. Primary sclerosing cholangitis (PSC) is a rare cholangiopathy of unknown etiopathogenesis and the role of CS in PSC has not yet been clarified. To evaluate hepatic expression of CS markers in PSC patients and its correlation with clinical-pathological features and prognosis.
Method: Thirty-five PSC patients (14 males, median age at diagnosis 27 years) followed-up for 12 (0.5–29) years with at least one available liver biopsy performed at diagnosis and/or during follow-up were retrospectively enrolled. Clinical, laboratory data, Mayo Risk Score (MRS) and Amsterdam-Oxford Model (AOM) at the time of liver biopsy were collected. The endpoint was survival without liver transplantation or cirrhosis decompensation. Grading and staging were assessed by 2 expert pathologists according to Nakanuma. Immunohistochemical stains for CS markers, p16 and p21, were performed and semi-quantitatively scored by a three-tier scale based on the positivity extent (negative, focal or diffuse) in native bile duct (NBD) and ductular reaction (DR).



Results: p16 expression in NBD and DR was directly correlated with hepatitis activity ($p = 0.02$ and $p = 0.05$), cholestasis-related histological lesions ($p = 0.09$ and $p < 0.001$), fibrosis ($p < 0.001$ for both) and disease stage ($p = 0.005$ and $p < 0.001$). p21 expression in NBD and DR was directly correlated with hepatitis activity ($p = 0.001$ and $p = 0.03$), cholestasis-related histological lesions ($p < 0.001$ for both), fibrosis ($p < 0.001$ for both) and disease stage ($p < 0.001$ and $p = 0.003$). By multivariate analysis p16 expression in DR was independently associated with advanced disease stages (HR 13.6 (95% CI 2.6–72.6), $p = 0.002$). p16 and p21 expression in DR was directly related to MRS ($p = 0.02$ for both) and AOM ($p < 0.001$ and $p = 0.007$). p16 and p21 expression in NBD was directly related to AOM ($p = 0.03$ for both). Finally, p21 expression in DR was independently associated with adverse outcome-free survival (HR 4.6 (95%CI 1.6–13.6) $p = 0.005$) (Figure).

Conclusion: In PSC CS marker expression is related to disease stage, clinical severity and prognosis, suggesting a role of senescence in the pathogenesis and progression of the disease.

THU130

Upregulation of hepatic TH17 response is associated with large duct disease and advanced hepatic fibrosis in pediatric autoimmune liver disease

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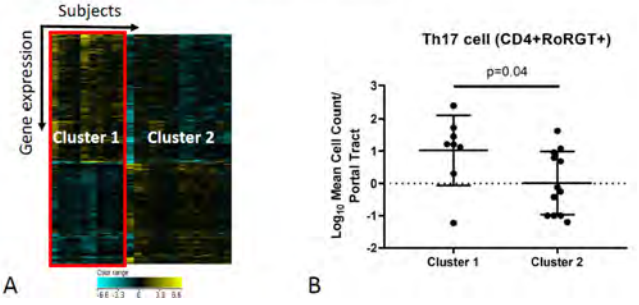
Background and Aims: In autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), and autoimmune sclerosing cholangitis (ASC), the presence of biliary injury portends a course refractory to medical therapy. We aimed to elucidate the predominant hepatic immune responses associated with biliary injury and fibrosis using RNA sequencing (RNAseq) and multi-parameter immunofluorescence (IF) on liver biopsy samples obtained at the time of a prospective research MRI.
Method: 24 subjects (male = 13, mean age = 15 y, PSC = 2, ASC = 10, AIH = 12) undergoing liver biopsy were prospectively enrolled. RNAseq was performed on liver tissue at a depth of 50 million reads with raw reads aligned to Hg38 using Kallisto. A moderated t-test was used to compare shared gene expression of protein coding transcripts. Magnetic resonance cholangiopancreatography (MRCP) and MR Elastography (MRE) were performed within a median of 23 days from biopsy. A radiologist and pathologist, both blinded to clinical and RNA data, classified MRCPs as abnormal in the presence of extra-/intrahepatic ductal dilatation or strictures and staged histopathologic liver fibrosis, respectively. Liver sections from 20 subjects underwent IF with antibodies against panCK, CD4, CD8, RoRGT, FOXP3 and TBET followed by image acquisition and automated quantitative image analysis.

Figure 1: (A) The unsupervised analysis of hepatic gene expression in 24 children with autoimmune liver disease identified two clusters of subjects with a share gene expression pattern. (B) Quantitative image analysis revealed a 7-fold increase in Th17 cells per portal tract in cluster 1 compared to cluster 2.



Results: An unsupervised analysis of liver RNAseq data identified two patient clusters (Figure 1A). Genes associated with IL17 responses and extracellular matrix remodeling were upregulated in cluster 1. By IF, although the frequency of CD4+ and CD8+ cells did not differ, there was a 4-, 7- and 9-fold increase in the frequency of IL17 (RoRGT+) producing cells, Th17 cells (CD4+RoRGT+) (Figure 1B) and Th17.1 cells (CD4+RoRGT+TBET+) per portal tract, respectively, in cluster 1 ($p < 0.05$ for all). The proportion of Th17.1 cells within the Th17 population was also higher in cluster 1 (73% vs 31%, $p < 0.001$). Importantly, MRCPs were abnormal in 10/10 patients in cluster 1

compared to 2/14 in cluster 2 ($p < 0.001$). 80% of subjects had a clinical diagnosis of PSC/ASC in cluster 1 vs 38% in cluster 2 ($p = 0.04$). Mean liver stiffness measurements by MRE (3.9 vs 2.8 kPa, $p = 0.02$) and Ishak histopathological stage of fibrosis (4.0 vs 1.8, $p = 0.003$) were also higher in cluster 1.

Conclusion: Large duct injury and advanced fibrosis in pediatric ASC and PSC is associated with an upregulation of the IL17 pathway, including pathogenic Th17.1 cells which are thought to be refractory to corticosteroid therapy. These RoRGT+ cells may represent novel therapeutic targets in pediatric patients with advanced PSC.

THU131

Elevated levels of systemic bacterial vesicles in autoimmune hepatitis are associated with non-response to corticosteroid therapy

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Background and Aim: Autoimmune hepatitis (AIH) is characterized by self-perpetuating immune-mediated inflammatory liver damage with or without fibrosis. Corticosteroids remain the main stay of treatment. Microbiome-liver axis has been recognised as a major modulator of autoimmunity and sepsis. We investigated the presence and activity of bacterial EVs in plasma and their interactions with immune cells in AIH patients and their association with steroid response.

Method: Fractionated pre-therapy plasma of AIH patients [n = 28, biopsy proven- noncirrhotic, F < 4, international simplified score $\geq$ 7, HAI score >4, ALT (148 ± 58.4 IU/ml), AST (140.7 ± 60.2 IU/ml){16 responders (R) and 12 non-responders (NR)] to corticosteroid therapy, and healthy controls (n = 12) for bacterial EVs [by ultracentrifugation using anti-OMPA (outer membrane protein A) and anti-LPS quantified using flow cytometry and western blot]. PBMCs of AIH patients were primed with bacterial vesicles (OMVs-2ug/ml) and (OMV+dynasore-80uM, to block the entry of OMVs inside the cells) for 24 hour and analysed for frequency, activation of total T (CD3+CD4+CD8+) cells, mucosal associated invariant T (CD3+CD161+TCRvα7.2+) cells, intracellular IL-17A and granzyme B release and B (CD19+) cells using multi-colour flowcytometry.

Results: Levels of systemic bacterial EVs (OMPA+LPS+) were higher in AIH patients than controls (28.3 ± 5.6 vs. 2.4 ± 1.1 EV/ul; $p < 0.001$), and were higher in moderate to severe than minimal to mild hepatic histological activity ($p = 0.042$). At baseline, NR to corticosteroids had higher bacterial EVs than R (39.6 ± 10.8 EV/ul vs. 12.4 ± 3.2; $p < 0.001$ with AUC = 0.71 CI [0.79–0.83]. Protein blots confirmed higher bacterial EV-associated LPS and OMPA in plasma fractions of NRs than R ($p = 0.003$). OMVs in NR PBMCs strongly stimulated the secretion of IL-17A ($p = 0.015$) and granzyme B ($p = 0.052$) from MAIT cells and also increased the frequency of activated MAIT cells (%MAIT+CD69+) ($p = 0.001$) than R. Even with OMV+ dynasore treatment, no inhibition was found in cytokine release in NR, suggesting overwhelming presence of OMVs in the cells of NR and continuous cellular activation.

Conclusion: Increased systemic OMPA and LPS-positive bacterial EVs are present at baseline in AIH patients and are able to induce marked immune activation through MAITs cells, which could contribute to corticosteroid resistance.

THU132

Single cell RNA sequencing reveals naive T cells ready for effector function in livers of patients with primary sclerosing cholangitis

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Background and Aims: Although genetic association analysis points towards immune dysregulation contributing to the pathogenesis of Primary Sclerosing Cholangitis (PSC), the role of specific immune cell populations within the liver of patients with PSC remains elusive. Here, we report on a comprehensive phenotypic and functional investigation of the liver infiltrating T cells of patients with PSC.

Method: Liver infiltrating and peripheral T lymphocytes were isolated from patients with PSC (n = 16) undergoing liver transplantation (LTX). As controls we used T cells from the same compartments from patients with alcoholic liver disease (ALD, n = 16) and blood of healthy donors (n = 10). Liver infiltrating T cells were sorted and processed for single cell RNA sequencing (scRNA-Seq) and cellular indexing of transcriptome and epitopes by sequencing (CITE-Seq). T cells from both compartments underwent flow cytometry-based deep immune phenotyping. Finally, naïve T cells were analyzed for proliferation capacity, cytokine production and differentiation capacity *in vitro*.

Results: By combining scRNA-Seq, CITE-Seq and multi-parameter flow cytometry, we observed a unique immunophenotype of liver infiltrating and peripheral T cells in PSC, when compared to ALD and healthy controls. A subset of liver infiltrating naïve-like $CD4^+$ T cells was identified in PSC patients with end-stage liver disease. Using flow cytometry, we confirmed the presence of phenotypically naïve $CD4^+$ T cells in PSC livers and found they were increased in frequency compared with ALD. Transcriptome analysis using scRNA-Seq revealed high expression of markers such as *STAT3* suggesting a possible predisposition to acquire a Th17 phenotype. *In vitro*, PSC-derived naive $CD4^+$ T cells showed higher rates of proliferation and production of cytokines associated with Th17 cells compared to healthy controls.

Conclusion: We here provide the first comprehensive atlas of intrahepatic T cells in PSC. Naïve-like $CD4^+$ T cells ready to differentiate into Th17 cells were identified within the liver and their abundance was increased in liver and blood of PSC compared to ALD. We propose these cells as potential contributors to disease pathogenesis.

THU133

Integrated analysis of GWAS and mRNA microarray identified IFN-? and CD40l as the central upstream-regulators in primary biliary cholangitis

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Background and Aims: Ten to 20% of patients with primary biliary cholangitis (PBC) are resistant to current standard therapy including ursodeoxycholic acid and progress to liver cirrhosis and hepatic failure. Therefore, there is a substantial need for novel treatments based on the pathogenesis of PBC through integrated pathway analysis with genes identified by GWAS and microarray.
Method: We performed the analysis of disease-pathways and their upstream-regulators by Ingenuity Pathway Analysis using the dataset 1 of GWAS (1920 PBC cases and 1770 controls) which included 261 annotated genes derived from 6760 SNPs (p-value<0.00001) and dataset 2 of mRNA microarray of liver biopsy specimens (36 PBC cases and 5 normal controls) which included 1574 genes (fold expression change>2, $p < 0.05$). Hierarchical clustering was performed using dataset 2. The genes identified in microarray were categorized into nine distinct cell types defined by a published data (Nat. Commun. 2018; 9:4383)).
Results: There were 27 genes (HLA, IKZF3, PRKCB, etc.) that were overlapped between the datasets 1 and 2, while there were 10 overlapped pathways (Th1, Th2 pathways, etc.) and 149 overlapped upstream regulators between the two datasets. Of these 149 upstream regulators, IFNG and CD40L were most significant among 7 upstream regulators that showed fold expression change >2 in the microarray. Hierarchical clustering divided the 36 patients into 2 clusters (Group 1 with higher- and Group 2 with lower- disease-activity). Most of the differently expressed genes between Group 1 and Group 2 belonged to the immune system and their upstream analysis predicted that IFNG and CD40L are the most significant upstream regulators among 40 regulators identified. In addition, we identified 10 and 7 downstream molecules of IFNG and CD40L, respectively, in cell type-specific manner. Of these downstream molecules, we found TNFRSF13C as a therapeutic target under clinical trials (e.g. VAY736) in sicca syndrome.
Conclusion: This study objectively identified the central role of IFNG and CD40L in both disease-susceptibility and -activity in PBC. In addition, new potential therapeutic targets were identified on pathways regulated by IFNG and CD40L.

THU134

FcRL4+ b cells are associated with inflamed bile ducts in patients with primary biliary cholangitis and locally capture IGA immune complexes

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Background and Aims: Primary biliary cholangitis (PBC) is an autoimmune liver disease characterised by an inflammatory infiltrate, leading to the slow and progressive destruction of the small bile ducts. The surface protein Fc Receptor-like 4 (FcRL4) is expressed by a subset of memory B cells. They were first identified in the mucosa-associated lymphoid tissue and are implicated in the pathogenesis of rheumatoid arthritis and Sjogren's syndrome. Here, FcRL4-expressing B cells were quantified in end-stage liver disease. Their localisation, rate of proliferation, differentiation stage, and the functional role of FcRL4 as an IgA receptor were investigated.
Method: Liver-infiltrating mononuclear cells were isolated from explant livers from patients undergoing liver transplantation at the Queen Elizabeth Hospital, Birmingham, UK. These cells were analysed using flow cytometry for markers of B cell differentiation, activation and proliferation. Immunohistochemistry staining of formalin-fixed paraffin-embedded (FFPE) sections was used to determine the localization of FcRL4-expressing cells.
Results: We have identified and characterised a population of $FcRL4^+$ B cells in end-stage liver disease.
In PBC ($n = 15$), $FcRL4^+$ cells represent 1.5% (median) of the total B cell population. This population is significant smaller in other end-stage liver diseases ($p = 0.0003$), including primary sclerosing cholangitis ($n = 14$), non-alcoholic steatohepatitis ($n = 10$), and polycystic liver disease ($n = 9$), as well as donor organs that did not meet criteria for transplantation ($n = 10$). Staining of PBC FFPE sections showed that the $FcRL4^+$ cells were found in close proximity to damaged biliary epithelium. When compared to $FcRL4^-$ B cells, the FcRL4 expressing B cells are highly proliferative, enriched for $CD11c^+CD21^-$ age-associated B cells and $CD27^+IgD^-$ class-switched memory cells, and expressed higher levels of co-stimulatory receptors CD80 and CD86. FcRL4 acts as a receptor for IgA aggregates and $FcRL4^+$ B cells were able to capture these aggregates both in vivo and in vitro. $FcRL4^+$ B cells were enriched for IgA^+ cells.
Conclusion: $FcRL4^+$ B cells were enriched around inflamed bile ducts in end-stage PBC. These B cells have an activated phenotype and the ability to harvest IgA immune complexes present in bile. The activity of $FcRL4^+$ B cells suggests a functional role in the local inflammatory IgA-mediated immune response and may contribute to PBC pathogenesis.

THU135

Bile from patients with chronic liver diseases activates MAIT cells

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Background and Aims: Chronic cholestatic liver diseases are characterized by progressive biliary inflammation leading to bile duct destruction and fibrosis. Mucosal-Associated Invariant T cells (MAIT cells) are a subset of innate-like T cells prevalent in human liver that recognize antigens presented by MR1. Although MR1 on the biliary epithelium is known to be able to present and active MAIT

cells, it is currently unclear if bile contains antigen activating MAIT cells. We aimed to determine if bile contains antigens that can be presented by cholangiocytes and activate MAIT cells.
Method: Bile samples were collected at the time of liver transplantation from 10 patients with primary sclerosing cholangitis (PSC, a chronic cholestatic liver disease), and 4 patients with other liver diseases serving as controls. PBMCs were isolated from healthy controls. Bile were either directly incubated with PBMCs, or with antigen presenting cells (THP1 and H69, a monocyte and cholangiocyte cell line) followed by washings and co-culture with PBMCs. MAIT cells activation was blocked with an anti-MR1 antibody (clone 26.5). Activation markers on MAIT cells were examined by flow cytometry.
Results: Four out of fourteen bile samples led to activation of MAIT cells in terms of increased Granzyme B expression when incubated with bile. The activation elicited by bile samples was partially MR1 restricted as it was partially blocked by an anti-MR1 antibody. Using serial dilutions of the bile samples a clear dose-response relationship was evident. The antigens in bile could also be taken up by THP1 cells and presented to MAIT cells. In the same manner H69 cells, representing the epithelial lining of the bile ducts, could take up and present antigens to MAIT cells.
Conclusion: Bile samples from patients with chronic liver diseases can contain MR1 restricted antigens that can be presented by cholangiocytes and activate MAIT cells. Their presence in bile can be due to bacteria or bacterial metabolites in bile, or a yet unknown endogenous antigen. These findings suggest that MAIT cells can take part in driving or modulating bile duct inflammation.

Cirrhosis and its complications: Experimental and pathophysiology

THU136
Inhibition of toll-like receptor 4 signaling reduces hyperammonemia by modulating urea cycle function

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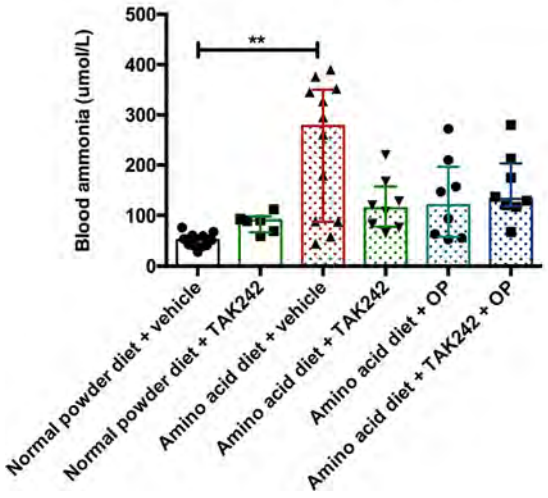
Background and Aims: The severity of hepatic encephalopathy is modulated by the synergistic effects of ammonia and inflammation. We have previously shown that administration of lipopolysaccharide (LPS) to cirrhotic animals is associated with hyperammonemia (HA), but the underlying mechanism is unknown. We hypothesized that the LPS/Toll-like receptor 4 (TLR4) axis modulates ammonia levels by impacting on the urea cycle and that inhibiting TLR4 may be a novel therapy for the treatment of HA.
Method: *Study 1 (LPS-induced HA)*: Cirrhosis was induced in rats by bile duct ligation (BDL), followed 4w later by 0.025 mg/kg LPS i.p. (n = 4–6). The TLR4 antagonist TAK-242 (10 mg/kg i.p.) was injected 3 hours before LPS (n = 7). *Study 2 (HA in TLR4 knock-out):* HA was induced by an amino acid diet (AA) for 14 days (10 g/20 g of normal powdered diet (NP)) in WT and TLR4$^{-/-}$ mice (n = 6–12). *Study 3 (TAK-242 in liver naïve HA):* HA was induced as in study 2. Mice were treated on day 10–14 with vehicle, 10 mg/kg TAK-242 i.p. or 0.3 g/kg Ornithine Phenylacetate i.p. (OP, ammonia scavenger, +control). Biochemistry and mRNA and protein expression of urea cycle enzymes (UCEs) was assessed.
Results: *Study 1:* Ammonia increased throughout sham, BDL and BDL +LPS ($p < 0.001$). TAK-242 was associated with a reduction in ammonia ($p < 0.01$) and higher coma-free survival (100% vs. 15%). Gene expression of all UCEs (particularly CPS1) decreased throughout sham, BDL and BDL+LPS (all $p < 0.05$), which was prevented by TAK-242 (all $p < 0.05$). *Study 2:* In WT mice, HA was induced by the AA diet vs. NP diet ($p < 0.01$). This effect was attenuated in TLR4$^{-/-}$ ($p = 0.059$). Protein expression of CPS1 was markedly upregulated in TLR4$^{-/-}$+NP as compared to WT+NP. *Study 3:* HA was induced by the AA diet and reduced by TAK-242 and/ or OP (Figure). CPS1 mRNA and protein expression was significantly increased in AA+vehicle ($p < 0.05$), but not in the TAK-242/ OP treatment groups. As the p53 pathway has been shown to be a regulator of ammonia metabolism by suppressing the UCEs, we showed in study 2 a downregulation of p53 mRNA in TLR4$^{-/-}$ mice relative to WT ($p < 0.05$) and in study 3 an upregulation in the AA+vehicle group ($p < 0.05$), which was attenuated by TAK-242 ($p < 0.01$) and OP ($p < 0.05$).

Figure: Inhibition of TLR4 signaling with TAK-242 reduces circulating ammonia levels in a liver naive model of hyperammonemia.



Conclusion: We show that TLR4 signaling contributes to the development of HA by modulating UCEs. The activation of the p53 pathway by ammonia may be involved as the underlying mechanism. TAK-242, a TLR4 inhibitor, is a potential novel therapy for HA.

THU137
Acute kidney injury is associated with reversible platelet dysfunction in hospitalized patients with decompensated cirrhosis

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Background and Aims: Recent evidence suggests that acute kidney injury (AKI) is the main predictor of post-paracentesis bleeding in patients with cirrhosis and ascites. With the hypothesis that the increased bleeding tendency in AKI is due to platelet dysfunction, we performed a prospective comparative study evaluating platelet function in patients with decompensated cirrhosis with and without AKI.
Method: Platelet function was assessed using whole blood lumiaggregometry to evaluate both platelet aggregation (an *in vitro* marker

Table: (abstract: THU137)

	AKI (n = 40)	**No AKI** (n = 40)	
Age (years)	56 (52–65)	57 (52–64)	
Male gender (%)	60	73	
Child-Pugh^	10 (7–13)	10 (7–12)	
Ascites (%)	83	85	
MELD score	25 (20–29)	18 (11–26)	
Previous decompensation (%)	90	85	
Total bilirubin, mg/dL	2.9 (1.9–4.7)	2.6 (1.5–5.8)	
INR	1.7 (1.4–1.8)	1.5 (1.3–1.8)	
Creatinine, mg/dL	1.8 (1.6–2.5)	0.8 (0.7–0.9)	
			p value
Platelet aggregation, Ω			
Collagen 1	12 (7–18)	16 (10–22)	0.03
Collagen 5	15 (11–20)	22 (15–27)	0.002
ADP	14 (9–18)	12 (9–18)	0.8
Platelet secretion, nmol			
Thrombin	0.28 (0.20–0.40)	0.57 (0.40–0.70)	<0.001
Collagen 1	0.12 (0.00–0.24)	0.34 (0.21–0.41)	<0.001
Collagen 5	0.22 (0.14–0.33)	0.48 (0.32–0.63)	<0.001
ADP	0.20 (0.10–0.27)	0.38 (0.26–0.61)	<0.001

of platelet response to vessel injury) and platelet secretion (an *in vitro* marker of granule release). Platelets were stimulated with collagen 1 μg/mL, collagen 5 μg/mL, ADP 10 μM and thrombin 50 μM. In patients with AKI, platelet function was re-evaluated after AKI resolution. Inpatients with AKI but without liver disease were included as controls.

Results: Eighty patients with decompensated cirrhosis were recruited (40 each with and without AKI). As shown in the table, Child class, type of decompensating event and platelet count were comparable in both study groups. Patients with decompensated cirrhosis and AKI had lower collagen-induced aggregation and lower collagen-, ADP-, and thrombin-induced secretion, indicative of a more severely impaired platelet function. With AKI resolution (n = 23/40), both aggregation and secretion recovered and became comparable to values in patients with cirrhosis without AKI. The impairment in platelet function in patients with cirrhosis and AKI as well as the significant improvement after AKI resolution were confirmed after adjusting the analysis for the severity of thrombocytopenia. Compared to healthy individuals, controls with AKI but without liver disease (n = 10) had significantly lower platelet aggregation and secretion.

Conclusion: In patients with decompensated cirrhosis, the presence of AKI is associated with significant platelet dysfunction that is fully reversible upon AKI resolution. These abnormalities likely contribute to the increased bleeding risk in these patients.

THU138

Different inflammasome activation predisposes for acute-on-chronic liver failure depending on hepatic compensation in human and experimental liver cirrhosis

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Background and Aims: Systemic inflammation predisposes acute decompensated (AD) cirrhosis to development of acute-on-chronic liver failure (ACLF), characterized by high mortality.
With supportive treatment, patients with AD can improve becoming recompensated. While AD is associated with ACLF development, little is known about the outcome of patients recompensated after an AD. In this study we hypothesize that proinflammatory markers such as IL-1alpha and IL-1beta predict development of ACLF in compensated and recompensated patients.

Method: 249 patients with cirrhosis were included and followed prospectively for fatal ACLF development. Patients were divided in compensated and recompensated (previous AD). Systemic inflammation was assessed by two inflammasome-driving interleukins (ILs): IL-1alpha (Caspase-4/11 dependent) and IL-1beta (Caspase-1 dependent). In rats, bile duct ligation was performed to induce cirrhosis and lipopolysaccharide exposition was used to induce AD and subsequent recompensation. IL-1alpha and IL-1beta serum levels and up- /downstream gene expression in liver and peripheral blood mononuclear cells were measured.

Results: Patients developing ACLF showed significantly higher baseline levels of IL. Recompensated patients and patients with detectable IL had higher rates of ACLF development than compensated patients. Baseline CLIF-C AD (HR 1.106), albumin (HR 0.872) and IL-1alpha (HR 1.248) were independent predictors of ACLF development in compensated patients; CLIF-C AD (HR 1.079) and IL-1beta (HR 1.184) in recompensated patients. Compensated rats showed significantly higher IL-1alpha gene expression and recompensated rats had higher levels of IL-1beta with higher hepatic gene expression.

Conclusion: Previous AD is an important risk factor for ACLF development and is possibly linked with inflammasome activation. The animal models confirmed the results of the cohort study showing

a link between ACLF development and IL-1alpha in compensated cirrhosis and IL- 1beta in recompensated cirrhosis.

THU139

Impaired splenic function in liver cirrhosis: a study in 69 patients with cirrhosis from outpatient hepatology clinic in a tertiary hospital in northern Greece

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Background and Aims: The role of the spleen as an important part of efficient immune response is more recognised over the last years. Our purpose was to investigate and quantify the degree of splenic dysfunction in patients with liver cirrhosis (LC) of various staging and etiology.

Method: 69 patients with LC were examined in hepatology clinic, at Papageorgiou Hospital, Greece, between 2014 and 2016. Diagnosis of cirrhosis was established through combination of laboratory findings (haematological parameters and imaging modalities) in the majority of cases.Liver biopsies were only performed for other indications. Etiology of cirrhosis was viral-28% (of which hep. B 52%), alcoholic-23%, NASH-14.3%, mixed –20.2%, autoimmune-7.2%, other-7.2%. Staging according to Child-Pugh (CP) score was: A-39%, B-41% and C-20%.

Splenic function was determined through pit cell count (PCC) and scintigraphy.

Samples of peripheral venous blood of 60 patients were examined in optical microscope, equipped with special lens and prism obtained especially for this research study. Number of PCC was calculated applying Differential Interference Contrast (D.I.C.) microscopy technique. A number of PCC above 2% was considered suggestive of splenic dysfunction, based on data from previous research.

All 69 patients underwent splenic scintigraphy with use of heat damaged, T99m-labelled red cells. Functional Splenic Volume (FSV-% uptake/ml) was calculated in all patients through SPECT/CT data analysis with use of specific software (OSIRIX). In addition, dynamic scintigraphy was performed in 27 patients, and the velocity of red cell clearance from circulation was calculated. Very few data was available regarding this advanced scintigraphic procedure and all parameters were calculated de novo.

Results: From D.I.C. microscopy, PCC percentage was >2% (diagnostic of spleen dysfunction) in 72% of patients with LC,ranging from 0.5% to 15% and there was a strong correlation between number of PCC and CP stage (p-value < 0.0001). From spleen scintigraphy, FSV was significantly decreased in patients with advanced LC compared to healthy subjects (ranging from 0.01%/ml to 0.33%/ml) and the correlation between FSV and CP score was statistically significant (p-value < 0.05).

Conclusion: As far as we are aware, our study was the largest including both calculation of pitted red cell count and performance of heat damaged, 99 m -labelled red cells scintigraphy in a population of patients with LC of various etiology and stages.

Splenic function is impaired in our population of patients with LC, regardless of etiology, and appears more significant in advanced stages (CT B and C). Splenic dysfunction and its potential implications need to be considered by clinicians managing patients with LC.

THU140

Histological characterization of muscle and adipose tissue in patients with cirrhosis receiving liver transplant

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Background and Aims: Body composition abnormalities are frequent in cirrhosis, and emerging evidence suggests that male sex is a risk factor for sarcopenia development and sarcopenia-related mortality, whereas female patients have a higher risk of losing subcutaneous adipose tissue in cirrhosis. Differences in skeletal muscle substrate metabolism by sex might contribute to this discrepancy. To better understand the pathophysiology of sarcopenia, sexual dimorphism in skeletal muscle fiber type and size as well as adipose tissue histological characteristics were investigated.

Method: CT images taken at the 3rd. lumbar vertebra were used to determine cross sectional areas of muscle, visceral and subcutaneous adipose tissue expressed by cm^2/m^2. Sarcopenia was defined as skeletal muscle index (SMI) <39 cm^2/m^2 in women and <50 cm^2/m^2 in men as published earlier. Biopsies of rectus abdominis muscle, periumbilical subcutaneous adipose tissue and visceral adipose tissue (omental) were obtained from the incision site at the time of liver transplant (LT) surgery. Muscle fiber boundaries were demarcated using laminin and dystrophin stain for muscle fiber size calculation. Fiber types were classified based on the isoforms of myosin heavy chain (MyHC). Adipose tissue sections were stained with Harris hematoxylin, and counterstained with eosin for histological analysis. Comparison between groups was made using Fisher's exact test and Mann-Whitney U test.

Results: Of 20 consented patients, 55% were male with a mean age of 50 ± 2 years, MELD score of 20 ± 1 points and mean BMI of 26 ± 1 (kg/m^2) at the time of LT. Sarcopenia was present in 60% of men and 33% of women. Lumbar SMI (cm^2/m^2) was significantly lower in sarcopenic patients compared to non-sarcopenic patients in both males (38 ± 2 vs. 60 ± 4; p = 0.001) and females (29 ± 9 vs. 44 ± 2; p = 0.049). No difference in mean muscle fiber area of total and per fiber type was observed by sex and sarcopenia. Sexual dimorphism was observed in the proportions of fiber types and MyHC isoforms (Figure). Percentage of MyHC type I (59% vs. 45%, p = 0.04) and consequently proportion of type I oxidative fibers (58% vs. 42%, p = 0.01) was higher in females compared to males. MyHC type IIA fibers, however, were more prevalent in males compared to females (55% vs. 40%, p = 0.009). Although visceral adipose tissue index (cm^2/m^2) tended to be higher in males (41 ± 9 vs. 22 ± 5; p = 0.09), no difference in the size of adipocytes by sex was observed for adipose tissue removed from visceral and subcutaneous depots (Figure).

Conclusion: Higher proportion of muscle type I oxidative fibers that are more resistant to atrophy in females might contribute to the sex differences in sarcopenia prevalence and related complications in cirrhosis.

THU141

A genetic risk score predicts de novo hepatocellular carcinoma in hepatitis C cirrotic patients treated with direct-acting antivirals

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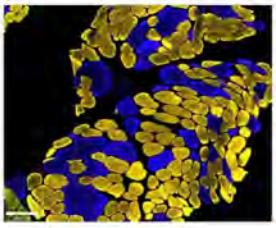
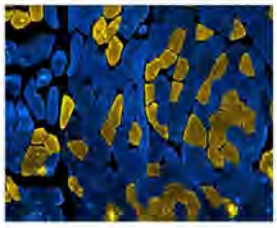
Histological Characteristics (mean± s.e.m)	Female (n=10)	Male (n=10)	P value
Total muscle fiber area (μm^2)	3604 ± 678	3866 ± 593	0.57
Fiber type I area (μm^2)	3051 ± 539	3506 ± 509	0.23
Fiber type I/IIA area (μm^2)	2239 ± 421	2901 ± 456	0.48
Fiber type IIA area (μm^2)	4584 ± 930	4469 ± 658	0.83
Fiber type IIA/D area (μm^2)	4291 ± 901	3785 ± 809	0.85
Fiber type IID area (μm^2)	2482 ± 416	2435 ± 457	0.81
Fiber type I (%)	58 ± 5	42 ± 6	0.01
Fiber type I/IIA (%)	1 ± 0.2	3 ± 1	0.23
Fiber type IIA (%)	26 ± 3	34 ± 5	0.31
Fiber type IIA/D (%)	13 ± 4	19 ± 5	0.51
Fiber type IID (%)	1 ± 1	3 ± 2	0.54
MyHC type I (%)	59 ± 5	45 ± 6	0.04
MyHC type IIA (%)	40 ± 5	55 ± 5	0.009
MyHC type IID (%)	15 ± 4	22 ± 6	0.63
Immunofluorescence staining of muscle samples for Myosin Heavy Chain type I (yellow) and type IIA (blue)			
Subcutaneous adipocytes area (μm^2)	1546 ± 290	1764 ± 199	0.60
Visceral adipocytes area (μm^2)	1007 ± 129	1085 ± 68	0.36

Figure: (abstract: THU140)

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Background and Aims: Several single nucleotide polymorphisms (SNPs) have been associated with hepatocellular carcinoma (HCC) in hepatitis C virus (HCV) cirrhotics, however their role in patients cured by direct-acting antivirals (DAA) is still undefined. We assessed the association between a genetic risk score (GRS) based on the combination of 4 SNPs (PNPLA3 rs738409, MBOAT7 rs641738, TM6SF2 rs5842926, GCKR rs1260326) and HCC in a cohort of DAA-treated patients.
Method: Consecutive HCV cirrhotics receiving DAA between December 2014–2016 in a single Center were genotyped. Cirrhosis was defined histologically or non-invasively (Liver stiffness measurement [LSM] ≥ 12 kPa). HCC was diagnosed and staged according to international recommendations. GRS score was calculated as already described.
Results: 509 patients were analyzed: median age 64 (28–87) years, 58% males, LSM 19.4 (12.0–75.0) kPa, 87% Child-Pugh score A (CPT) A. Genotypes distribution was as follows: PNPLA3 CC (46%), CG/GG (54%); MBOAT7 CC (29%), CT/TT (71%); TM6SF2 CC (91%), CT/TT (9%); GCKR CC (26%), CT/TT (74%). Median GRS score in the overall population was 0.3 (0–1.1). Patients' main clinical features were similar across SNPs genotypes. During a median follow-up of 43 (3–57) months from DAA start, de novo HCC developed in 36/452 (8%) patients, 4-year estimated cumulative probability of HCC being 9% (95% CI 7–12%). Male sex (Hazard Ratio [HR] 2.54; 95% CI 1.15–5.63; p = 0.02), diabetes (HR 2.39; 95% CI 1.20–4.74; p = 0.01), albumin (HR 0.35; 95% CI 0.19–0.64; p = 0.001) and GRS score >0.6 (HR 2.30; 95% CI 1.03–5.11; p = 0.04) were independently associated with de novo HCC. Indeed, 4-year cumulative rates of HCC resulted 6% vs. 12% in males vs. females (p = 0.01); 17% vs. 7% in diabetic vs. non-diabetic (p = 0.001); 21% vs. 7% in patients with albumin ≤ or >3.5 g/dl (p < 0.001) and 16% vs. 7% in patients with a GRS score > or ≤0.6 (p = 0.01), respectively. By combining independent risk factors for HCC, 4-year cumulative incidence resulted 20% vs. 5% in patients with or without two different risk factors, respectively (p < 0.0001).
Conclusion: In a large, single-center cohort of consecutive HCV cirrhotic patients treated with DAA, a genetic risk score was independently associated with de novo HCC, together with clinical predictors (male sex, diabetes, albumin values). Combination of clinical and genetic predictors could allow better HCC risk stratification at the individual level.

THU142

The bone marrow pool of megakaryocytes and their ability to proliferate are preserved in rats with advanced cirrhosis

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Background and Aims: Hypersplenism is considered the main factor responsible for thrombopenia in cirrhosis. Recent studies suggest that additional mechanisms leading to reduced platelet production may also contribute as liver disease progresses. Our **Aim** was to comprehensively assess the peripheral and central factors responsible for platelet production in experimental liver disease.

Method: Cirrhosis was induced in male SD rats (200 gr bw) by oral gavage with carbon tetrachloride (CCl4) b.i.w for 4, 8 and 12 weeks. Control rats received water (H2O) instead of CCl4, and all rats had phenobarbital (35 mg/dl) in drinking water. In an additional set, animals receiving H2O or CCl4 for 12 weeks were administered a s.c. dose of Romiplostim (thrombopoietin (TPO) agonist) or Vehicle and they were euthanized 6 days later. Liver disease was evaluated by blood cell count, biochemistry and coagulation analyses, liver- and spleen- to-bw ratios, histology (H&E and Sirius Red), and by a hemodynamic study to measure portal pressure (ileocolic vein). The mRNA expression of *Tpo* and its receptor *Mpl* were quantified in liver and bone marrow by real time RT-PCR with Taqman probes. The levels of TPO in arterial blood and regional venous beds were measured by ELISA. Bone marrow from femur and tibia was FFPE and megakaryocytes were counted in H&E-stained sections (total surface = 2 mm^2/rat).

Results: CCl4-treated rats progressively developed liver disease, presenting at 12 weeks advanced micronodular cirrhosis, liver atrophy (Liver-to-BW ratio (%): 3.61 ± 0.32 vs 2.64 ± 0.24, $p < 0.01$), splenomegaly (Spleen-to-BW ratio (%): 0.15 ± 0.04 vs 0.39 ± 0.10, $p < 0.001$), thrombopenia ($x10^9$/L: 650 ± 137 vs 343 ± 244, $p < 0.05$), coagulopathy (INR, $p < 0.01$), and high portal pressure (mmHg: 6.16 ± 1.08 vs 11.70 ± 2.84, $p < 0.01$). At this time, *Tpo* mRNA expression was unchanged and *Mpl* mRNA was increased ($p < 0.05$) in liver, whereas both *Tpo* and *Mpl* mRNA expressions were reduced in bone marrow (both $p < 0.05$) of CCl4-treated rats. The arterial concentration of TPO was similar in H2O- and CCl4 groups (pg/ml: 146 ± 38 vs 174 ± 38, $p = 0.24$), and the regional A-V differences supported a TPO efflux from the liver and net uptake in bone marrow (femoral vein). Megakaryocyte counts in CCl4-treated rats were similar or even tended to be higher than in Control rats at all time points. Romiplostim induced important elevations of circulating platelets and megakaryocyte cell counts in both groups, but the platelet cell count still remained lower in CCl4-treated rats ($p < 0.001$).

Conclusion: The pool of bone marrow megakaryocytes and their ability to proliferate are not reduced in rats with advanced liver disease. Therefore, inadequate levels of circulating TPO relative to platelet cell count and/or intrinsic impairment of platelet production by megakaryocytes are the two mechanisms that could explain a potential impairment of platelet production in advanced cirrhosis.

THU143

Bile acids modify ROS production, impair chemotaxis and delay apoptosis of neutrophils in vitro

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Background and Aims: Immune dysfunction is a life-threatening problem for liver cirrhotic patients. The pathophysiology of neutrophil function changes in these patients, which lead to the increased risk of bacterial infections, is still to be explained. Bile acids (BA) are highly elevated and composition is altered in liver cirrhosis. BA were shown to play a role in multiple processes in human organism, including immune response. We hypothesize that BA in the concentrations found in systemic circulation of liver cirrhotic patients can influence neutrophil function.

Method: Human neutrophils were isolated from peripheral blood of healthy volunteers with Percoll gradients. ROS (reactive oxygen species) production was assessed after 45 min BA (Sigma-Aldrich, Vienna, Austria) pre-treatment of TNFalpha primed or mock primed neutrophils and stimulation or not with fMLP (N-formyl-met-leu-phe). Cells were mixed with HRP (horseradish peroxidase) and luminol and total ROS production was measured in real-time by chemiluminescence. Chemotaxis towards fMLP of BA treated neutrophils was measured with ChemoTX disposable chemotaxis systems (Neuro Probe, Gaithersburg) and ibidi chemotaxis chambers (ibidi GmbH, Gräfelfing). Flow cytometry analysis of Annexin/PI stained neutrophils was used to assess the amount of necrotic and apoptotic cells.

Results: BA mix ($p = 0.003$) containing 15 BA in the concentrations found in liver cirrhotic patients (cholic acid (CA), chenodeoxycholic acid (CDCA), lithocholic acid (LCA), deoxycholic acid (DCA), ursodeoxycholic acid (UDCA) and their tauro and glyco conjugates) stimulated ROS production in neutrophils. DCA, CDCA and LCA had a tendency to inhibit fMLP stimulated ROS production. DCA ($p = 0.043$), CDCA ($p = 0.030$), LCA ($p = 0.018$) and their tauro and glyco conjugates, tauro ($p = 0.014$) and glyco ($p = 0.044$) ursodeoxycholic acids (UDCA) significantly decreased chemotaxis of neutrophils up to 90% in response to fMLP. Glyco CDCA interfered significantly with chemotactic directionality ($p = 0.030$). BA mix ($p = 0.013$), LCA ($p = 0.042$), CDCA ($p = 0.015$), UDCA ($p = 0.032$) delayed neutrophil apoptosis.

Conclusion: BA in the concentrations found in liver cirrhotic patients modify neutrophil ROS production, impair chemotaxis and delay apoptosis. Increased BA levels and altered composition in liver cirrhosis can therefore be the reason for the neutrophil dysfunction and prospective target for prevention of bacterial infections in these patients.

THU144

Neuro and hepatic inflammation and steatosis are modulated by gut microbial changes after isolated hepatic vagotomy and antibiotics in cirrhosis

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Background and Aims: Cirrhosis & hepatic encephalopathy (HE) includes an altered gut-liver-brain axis. While microbiota changes in germ-free mice have been described, the role of individually isolating the liver-brain axis & microbial alterations is unclear.

Aim: Define the effect of non-absorbable antibiotics (NAbx) & isolated hepatic vagotomy on gut microbiota, liver inflammation and brain inflammation in the setting of cirrhosis.

Method: 10 wk old C57BL/6 mice were divided into conventional (Conv) & those with isolated hepatic vagotomy (Vago, Fig 1A). Subgroups from both were gavaged with CCl4 for 12 wks to develop cirrhosis. After cirrhosis, Conv & Vago cirrhotic subgroups were further treated with 2 wks of Streptomycin+Polymyxcin B(NAbx). All gps were sacrificed at 14 wks & frontal cortex, colon & liver were harvested. Data were compared between groups.

Microbiota: 16sRrNA sequencing of colon. *Neuro-inflammation*: qRT-PCR of mRNA expression of inflammation (MCP-1), microglial activation (IBA-1). *Liver inflammation/histology*: A blinded pathologist determined steatosis & inflammation grades. qRT-PCR mRNA levels of SREBP1c, MCP-1 & fatty acid oxidation enzyme stearoyl-CoA desaturase 1(SCD-1) were performed.

Results: No behavioral changes were seen & all mice lived till sacrifice at 14 wks.

Microbiota: Conv cirrhosis has higher dysbiosis with ↓beneficial (Lachnospiraceae & Ruminococcaceae) & ↑ pathobionts (Enterobacteriaceae) vs controls. NAbx ameliorated this dysbiosis. Vagotomy was related to lower dysbiosis with ↑beneficial taxa at baseline, after cirrhosis & even after NAbx compared to conv mice at similar stages.

Brain: Neuro-inflammation: Significant ↑ in MCP-1 which occurred post-cirrhosis in conv & Vago mice were reduced after NAbx (Fig B).

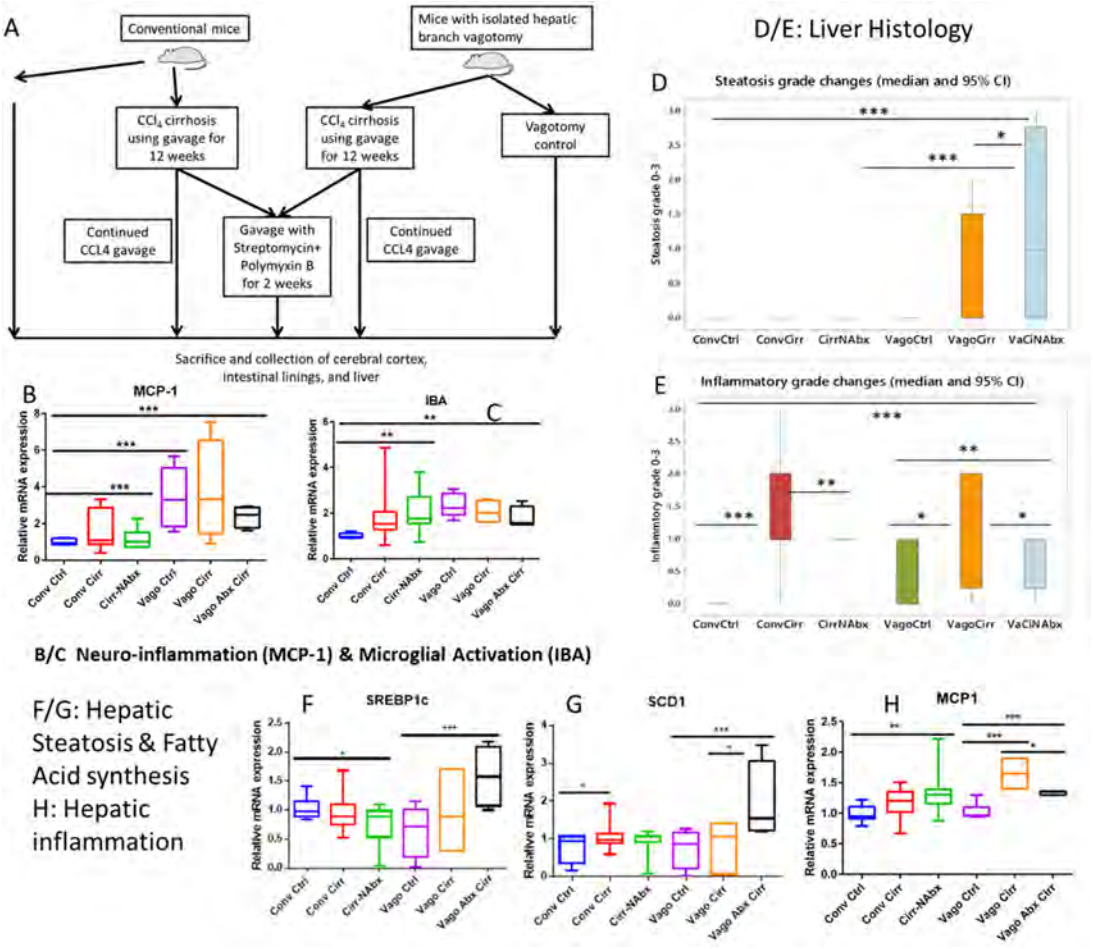

Figure: Overview and Results of Experiment. ***p < 0.001, **p < 0.01.

Microglial activation: IBA ↑ post-cirrhosis in conv mice & was ↓ postNAbx but vagotomy completely abolished this activation (Fig C). *Liver*: *Histology*: No steatosis was seen in conv mice groups but this increased post-Vago cirrhosis & was highest after NAbx in Vago-cirrhosis. Inflammation was seen post-cirrhosis in Conv mice, which reduced post-NAbx. Inflammation was higher at baseline in Vago, ↑ post-cirrhosis & ↓post-NAbx(Fig D/E). *mRNA*: SREBP1c &SCD-1 increased post-Vago cirrhosis & even further post-NAbx (Fig F–G). MCP-1 also worsened post-vago cirrhosis and ↓postNAbx (Fig H).
Conclusion: Liver-specific vagotomy is associated with lower gut dysbiosis, greater liver inflammation and steatosis, neuro-inflammation despite the abolition of microglial activation in mice with cirrhosis. Additive NAbx improves liver and brain inflammation but worsens steatosis after vagotomy. Liver and brain inflammation are independently important targets, in addition to the microbiota, in beneficially modulating the gut-liver-brain axis in cirrhosis

THU145
Effective albumin concentration and albumin function improve after long-term albumin treatment in patients with decompensated cirrhosis

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Background and Aims: In addition to its oncotic power, human albumin (HA) carries several other biological functions supporting the pleiotropic activity of the molecule. The ANSWER trial[1] showed that long-term HA administration in patients with cirrhosis and uncomplicated ascites improves overall survival and reduces the incidence of complications. Such benefits were associated to a significant increase in serum albumin concentration. The present ancillary study to the ANSWER trial aimed to assess whether long-term HA administration has any effect on both structure and function

of the circulating HA pool and on the pro-inflammatory state that characterized decompensated cirrhosis.
Method: Patients from the ANSWER cohort with available plasma samples at baseline and 6–8 months after randomization were included in the study. HA structural microheterogeneity was evaluated by liquid chromatography/electrospray ionization mass spectrometry. Effective albumin concentration was defined as the amount of serum albumin with fully preserved molecular structure. Binding efficiency (BE) and detoxification efficiency (DTE) were determined by electron paramagnetic resonance spectroscopy. A panel of circulating cytokines was measured by Luminex assay.
Results: Twenty-seven patients from the standard medical treatment (SMT) and 31 from the SMT+HA arms were included in the analysis. Baseline clinical and biochemical characteristics were comparable between the two groups. Serum albumin concentration increased significantly after 6–8 months of HA treatment (from 3.1 [2.8–3.5] to 4.1 [3.8–4.4] g/dL, $p < 0.001$) but not in the SMT arm (from 3.0 [2.8–3.4] to 3.1 [2.6–3.8] g/dL, $p = 0.846$). Similarly, significant rises of the effective albumin concentration (from 0.77 [0.55–1.05] to 0.93 [0.65–1.26] g/dL, $p = 0.015$) as well as both BE (+16.8 [3.7–31.12] %, $p < 0.001$) and DTE (+15.4 [5.5–41.7] %, $p < 0.001$) were only found in the SMT +HA arm. Finally, circulating pro-inflammatory cytokines, such as interleukin (IL)-6 and IL-33, were significantly reduced only in patients from the SMT+HA arm.
Conclusion: Besides the rise in the serum albumin concentration, long-term HA treatment significantly increases the amount of the effective albumin concentration, corresponding to the fraction of the circulating albumin pool with a fully preserved structure. This finding was associated with an improvement of the albumin binding/detoxification dysfunction and systemic inflammation.

Reference

1. *Lancet* 2018;391:2417–29.

THU146

SLU7 downregulation potentiates liver damage through hepatic de-differentiation

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Background and Aims: The splicing factor SLU7 plays a central role in liver homeostasis securing the transcriptional program characteristic of the functional and quiescent adult liver. SLU7 downregulation induces a transcriptional switch characteristic of the fetal and transformed hepatocyte including the promotion of the fetal Hnf4alpha P2 promoter. As a result, SLU7 knockdown impairs liver metabolic functions and induces aerobic glycolysis and liver growth. Furthermore, SLU7 is required to preserve genome stability. SLU7 expression is reduced in the liver of cirrhotic patients, suggesting a role in the loss of hepatic functions observed in these patients. In the present work we aim to study the contribution of SLU7 downregulation to the hepatic response to damage.
Method: Chronic liver damage was induced by 6 weeks CCl4 administration to wild-type (SLU7 +/+) and SLU7 haploinsufficient (SLU7 +/–) mice. Acute liver damage was induced upon acetaminophen (APAP) administration. SLU7 was overexpressed using an adeno-associated virus (AAV-SLU7). Serum transaminases were measured, and hematoxylin-eosin and Sirius red staining were performed. Gene expression was studied by qPCR, Western blot and IHQ.
Results: Hepatic SLU7 expression was reduced after CCl4-induced chronic damage parallel to an induction of the fetal Hnf4a-P2 promoter, also observed in the liver of cirrhotic patients. SLU7 +/– mice showed significantly higher levels of serum transaminases, larger areas of necrosis and higher activation of hepatic stellate cells resulting in an increased expression and deposition of collagen. These events were accompanied by increased oxidative stress, a significantly higher activation of HNF4a-P2 promoter and the decrease of several liver specific genes. Accordingly, we found that SLU7 overexpression significantly attenuated chronic liver damage, impairing the induction of oxidative stress, the activation of HNF4a-P2 and the inhibition of hepatocyte specific genes. APAP-induced acute liver damage in wild type mice transiently reduced hepatic SLU7 expression. Liver damage was again significantly increased in SLU7 +/– mice as evidenced by serum transaminases and histology analysis. SLU7 +/– mice exhibited higher levels of oxidative stress, an induction of HNF4a-P2 activity, a reduction in glycogen content, a sustained expression of CYP2E1 and a reduction in CYP3A4 expression. The administration of AAV-SLU7 significantly attenuated APAP these events.
Conclusion: SLU7 downregulation contributes to liver damage. Mechanistically this can be associated to the reprograming of liver transcriptome and the induction of fetal isoforms including those expressed from HNF4a-P2 promoter resulting in an increased oxidative stress.

THU147

Endotrophin predicts clinical outcome and mortality in patients with compensated cirrhosis

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Background and Aims: Prediction of hard endpoints is important for optimal patient management. Endotrophin, a hormone derived from type VI collagen and produced by fibroblasts, has previously been associated to liver fibrosis. Here we investigated if PRO-C6, a serological biomarker of endotrophin, could predict clinical outcome and mortality in a compensated cirrhosis cohort.
Method: 172 patients with mixed aetiology of cirrhosis were consecutively recruited from the Nottingham compensated cirrhosis cohort study (3CN). Patients were assessed for clinical outcomes using digital hospital records or contacting primary care physicians. Primary Liver Outcome (PLO) was defined as first event of ascites, variceal bleed, encephalopathy, HCC, or liver related death. Any outcome (AO) was defined as first event of PO, death, decompensation, jaundice or liver transplantation. Death was defined as either overall survival (OS) or liver related mortality (LRM). PRO-C6 was assessed in serum at baseline and compared to Model for End-Stage Liver Disease (MELD).
Results: The cohort included 64% males; mean age of 59.6 years with mixed etiology of alcoholic (40%), non-alcoholic (33%), autoimmune (12%) or viral liver disease (15%). Mean time to first event was 3.9 years. No difference in PRO-C6 levels was observed between etiologies ($p = 0.201$), thus were pooled for further analyses. PRO-C6 levels were significantly elevated in patients with PLO, AO and OS ($p < 0.0001$). Cox regression analyses showed that both PRO-C6 and MELD were independent predictors of clinical outcome and survival. Kaplan-Meier analyses showed that PRO-C6 levels above the median predicted poorer clinical outcome (PLO: HR = 3.4, $p < 0.001$; AO: HR = 3.2, $p < 0.001$), and shorter survival time (LRM: HR = 3.2, $p < 0.05$; OS: HR = 2.9, $p < 0.05$). Similar differences were found for MELD above the median. Combining the two markers further improved the prognostic value (PLO: HR = 19.5, $p < 0.0001$; AO: HR = 11.9, $p < 0.0001$), and

shorter survival time (LRM: HR = N/A, p < 0.01; OS: HR = 13.6, p = 0.001).
Conclusion: Endotrophin (PRO-C6) is associated with clinical outcome and survival independent of MELD and provides prognostic value for compensated cirrhosis patients. This suggests that collagen signals are important drivers of disease progression in patients with chronic liver disease.

THU148
Characterization of lymphocyte subsets in ascites during spontaneous bacterial peritonitis: MAIT cells show the strongest increase
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Background and Aims: Patients with advanced liver cirrhosis have an increased susceptibility to bacterial infections such as spontaneous bacterial peritonitis (SBP). As part of the cirrhosis-associated immune dysfunction present in these patients, mucosal associated invariant T (MAIT) cells, that have the capacity to respond towards bacteria, are severely diminished in circulation and liver tissue. However, the role of MAIT cells in decompensated cirrhosis, especially in the peritoneal cavity and during SBP, remain elusive. In this study, we aimed to investigate the immune compartment of patients with decompensated cirrhosis and SBP and reveal differences between SBP and Non-SBP patients.
Method: Matched peripheral blood and ascites fluid from 35 patients with decompensated cirrhosis, with or without spontaneous bacterial peritonitis were analyzed. Lymphocyte subsets as well as monocyte subsets were determined and phenotype and function were analyzed using high-dimensional flow cytometry. Obtained data were also compared to blood samples of healthy controls (n = 24) and compensated cirrhosis patients (n = 11).
Results: Among all immune subsets analyzed in ascites**,** MAIT cells (CD161+ Vα7.2+ CD4-) were the most enriched population in SBP versus non-SBP. MAIT cell percentages as well as total numbers were significantly increased in the peritoneal cavity of patients with SBP (p = 0.004; p = 0.008 respectively). MAIT cells isolated from non-infected ascites show an activated tissue resident phenotype. This phenotype was not significantly altered during SBP. Compared to the decreased and impaired MAIT cells isolated from blood, peritoneal MAIT cells show higher cytokine responses to in-vitro stimulation with *E. coli* or IL-12 + IL-18. This was not diminished during SBP.
Conclusion: Despite severely diminished MAIT cell numbers and impaired phenotype in circulation, peritoneal MAIT cells remain abundant, activated, and highly functional in decompensated cirrhosis and are the most increased lymphocyte population in SBP. This suggests that peritoneal MAIT cells could be a potential target for immune intervention strategies in patients with decompensated liver cirrhosis and SBP.

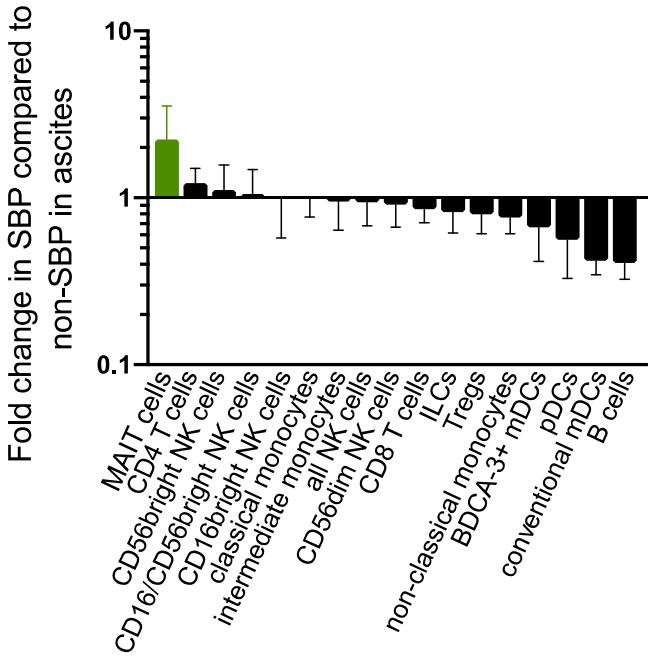

Figure: (abstract: THU148)

THU149
Immune cell response in progressing liver cirrhosis is dominated by neutrophil granulocytes
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Background and Aims: Progression of liver cirrhosis is associated with systemic inflammation leading to further tissue injury. Little is known about the immune cell phenotype in acute decompensation (AD) and acute-on-chronic liver failure (ACLF). This study aimed at analysing the pattern of immune cell subsets in blood samples of patients with progressing liver cirrhosis.
Method: 63 blood samples of patients with AD (n = 50) or ACLF grade 1 (n = 13) were collected retrospectively from patients' records. Leukocyte subpopulations were identified by flow-cytometry using forward and sideward scatter and markers of lymphocyte (LY) subsets: CD3 T-cells, CD4 T-helper cells, CD19 B-cells, CD8 cytotoxic T-cell, CD16/56 NK-cells. The function of neutrophil granulocytes (NG) was assessed by phagocytosis (PA) and oxidative burst activity (OBA) assays. Values were expressed as median [range].
Results: ACLF patients had a higher MELD Score (p = 0.0022) and tended to have higher CRP level (p = 0.0722) and white blood cell count (WBC) (p = 0.12) compared to AD patients. As a sub-analysis of the AD cohort, we considered the CLIF-C AD score to distinguish between high (CLIF-C AD ≥ 60), medium (CLIF-C AD45–60) and low risk (CLIF-C AD≤45) liver disease progression. There was a stepwise increase of the aforementioned parameters except for CRP level throughout CLIF C AD groups (MELD p = 0.0015, CRP p = 0.29, WBC p = 0.009). NGs were significantly higher in patients with ACLF compared to AD (ACLF 4.87 10^9/l [2.9–26.3], AD 3.1 10^9/l [1.7–10.70], p = 0.0119) whereas LY subpopulation were unaltered. This finding was underlined by a higher NG/LY ratio of 8.86 10^9/l [3.25–13.80] in ACLF compared to 4.170 10^9/l [1.4–22.6] (p = 0.0040) in the AD cohort. NG of 4.9 10^9/l [2.4–11.3] were also significantly increased in CLIF-C AD ≥ 60 patients compared to 3.05 10^9/l [1.7–12.4] in CLIF-C AD45–60 and 2.3 10^9/l [1–3.7] CLIF-C AD≤45 (p = 0.0013). The same

effect was detectable for the NG/LY ratio with values of 5.38 10^9/l [2.4–22.66], 4.32 10^9/l [2.1–13.5] and 2.33 10^9/l [1.4–12] (p = 0.0466), respectively. The number of NG correlated positively with the Organ failure score (r = 0.2774, p = <0.001) MELD Score (r = 0.1957, p = 0.0005), Child-Pugh Score (r = 0.1653, p = 0.0015) and CLIF-C AD-Score (r = 0.1887, p = 0.0006). No such changes were found in LY or the other mentioned subpopulations. Analyses of PA and OBA of NG showed no significant loss of function in the ACLF and AD cohort (OBA p = 0.1813, PA p = 0.2323).

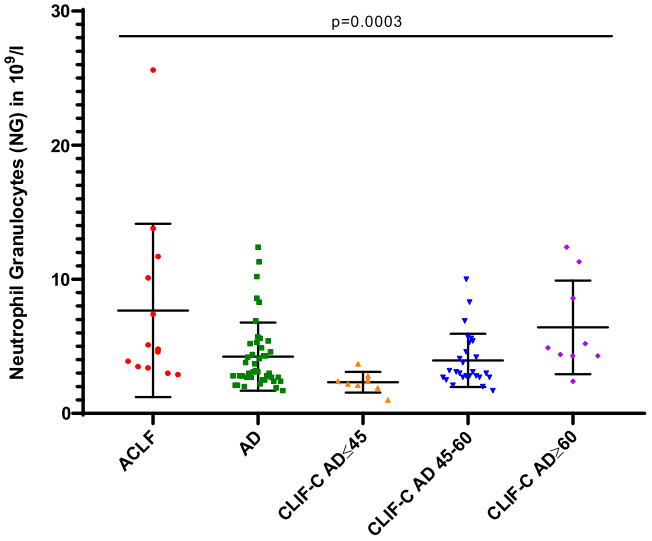

Figure: NG in patients with ACLF, AD and subgroups of AD defined by CLIF-C AD score.

Conclusion: The progression of liver cirrhosis in AD and ACLF is associated with an immune cell pattern dominated by NG whilst LY remain unchanged. PA and OBA seem to be unaffected by the severity of liver disease probably due to lack of high-grade ACLF patients. Further studies are needed to clarify the role of NG and its impact on liver disease progression.

THU150

Proagio: a protein designed to target integrin alpha V beta 3 outside ligand binding site is an effective way to target activated hepatic stellate cells

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Background and Aims: Chronic Liver Diseases (CLDs) arise from the persistent inflammatory response to injury within the liver parenchyma leading to the activation of hepatic stellate cells (HSCs) leading to uncontrolled secretion and accumulation of fibrillar collagen, in the space of Disse. Accompanying ECM secretions are neo-angiogenesis and sinusoidal remodeling. HSC activation and their subsequent resistance to apoptosis. Accumulation of collagen fibrils is characterized by the presence of a fibrotic scar which disrupts hepatic architecture and its function. The scar alters the structure of the sinusoidal space thereby increasing blood flow resistance and portal hypertension. Here we report a novel approach to induce HSC apoptosis via integrin αVβ3 using a rationally designed protein, ProAgio, to target a non-canonical binding site. ProAgio specifically targets integrin αVβ3 at a novel site thus triggering apoptosis thereby providing a viable treatment option for the progression of CLDs. Aim: To test the efficacy of ProAgio treatment on the reversal of fibrosis and changes in the portal pressure.

Method: To study the expression of integrin αVβ3 and the capability of ProAgio to induce apoptosis, we used mouse models of liver fibrosis, namely, (A) i.p. thioacetamide (TAA) with 10% ethanol in drinking water ad libitum and (B) Oral carbon tetrachloride (CCl4) were used for testing the effect of ProAgio (10 mg/kg) *in vivo*.
Results: Activated HSCs upregulate integrin αVβ3. ProAgio induces apoptosis in activated HSCs via an integrin-mediated death (IMD) like mechanism. During the advent of liver fibrosis, the persistent pro-inflammatory state leads to the pathological activation of HSCs, thereby leading to the aberrant synthesis and accumulation of collagen, this deposition in the sinusoidal space alters the hepatic structures and function, ultimately leading to CLDs. Treatment with ProAgio starkly induced apoptosis in these activated HSCs in in vitro and in vivo model. Mice treated with ProAgio showed reduced activation and increased apoptosis of HSCs in the hepatic parenchyma. HSC apoptosis consequently reduced collagen synthesis and accumulation. ProAgio brings a novel therapeutic option for the treatment of CLDs.
Conclusion: In both the pre-clinical advanced cirrhotic mouse models (TAA and CCl4), ProAgio treatment has demonstrated great efficacy in liver fibrosis reversal and decreased portal hypertension.

THU151

Hepatocytes undergo pyroptosis in response to lipopolysaccharide exposure, and can be sensitised to cell death by ER stress

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Background and Aims: Acute-on-chronic liver failure (ACLF) is a common cause of mortality in cirrhosis. Systemic inflammation and non-apoptotic hepatocyte cell death are key features of ACLF. We have previously shown that hepatocyte pyroptosis, an inflammatory mode of cell death occurring in response to bacterial endotoxin (LPS) exposure, is a key feature of ACLF and correlates with disease severity (Soffientini et al 2018). Additionally, cirrhotic mice demonstrate greater sensitivity to LPS exposure, with greater levels of hepatocyte cell death, than non-cirrhotic mice (Soffientini et al 2019). The aim of this study was to determine potential mechanisms of sensitization to hepatocyte pyroptosis in vitro.
Method: Primary human hepatocytes (Lonza Biologicals, UK), or Huh7 (human) and AML12/BNL1MA.7R.1 (murine) hepatocyte cell lines were used for all experiments. All cell experiments were repeated 3–5 times. Cells were exposed to LPS from Klebsiella pneumoniae (Merck, UK) at a very low-dose LPS (0.1–1μg/ml) for 24 hours to mimic gut bacterial LPS translocation. In some experiments, cells were also exposed to a ER stress inducer for 24 hours along with very low-dose LPS (tunicamiycin or brefeldin A, Merck, UK). Subsequently cells were treated with a LPS "hit" (6–100 mg/ml) to induce pyroptosis. Caspase-4/11 activation was assessed by Western blot. Pyroptosis was assessed by cleavage of the effector protein Gasdermin D (GSDMD) by Western blot. Total cell death was assessed by LDH release (Promega LDH-Glo assay).
Results: Human and murine cell lines undergo GSDMD cleavage in response to LPS exposure; Huh7 cells: LPS group vs control, p = 0.065; BNL cells: LPS group vs control, p = 0.085. LDH release was also increased in hepatocyte cell lines; Huh7: LPS group vs control, p = 0.07, BNL cells: LPS group vs control, p < 0.01. Huh7 primed for 24 h with very low-dose LPS (1 μg/ml) and the ER-stress inducer tunicamycin show increased susceptibility to subsequent LPS 'hit' (30 μg/ml; 4 h) compared to LPS hit alone, very low-dose LPS alone or tunicamycin alone (Figure, ANOVA with post-hoc test, p < 0.01). These experiments were replicated in primary human hepatocytes primed for 24 h with very low-dose LPS (100 ng/ml) and tunicamycin, showing susceptibility to a LPS hit (6 μg/ml) (ANOVA with Tukey

post-hoc test, $p < 0.05$). The mechanism of LPS/ER stress priming is through caspase-11 activation: AML cells primed for 24 h with very low-dose LPS (1 μg/ml) and tunicamycin demonstrate activation of caspase-11 compared to tunicamycin or very low-dose LPS alone (ANOVA with post-hoc test, $p < 0.01$).

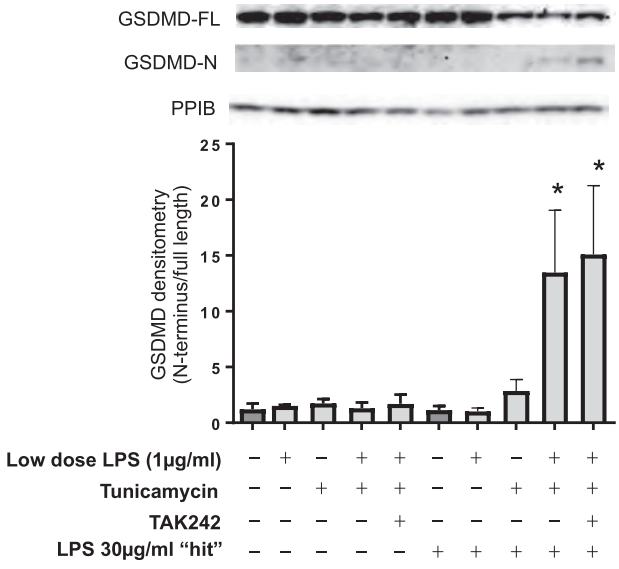

Figure: (abstract: THU151)

Conclusion: ER stress and gut bacterial LPS translocation are features of cirrhosis. These data demonstrate that ER stress and very low-dose LPS exposure sensitize hepatocytes to undergo pyroptosis in response to an LPS 'hit.' This mechanism may underlie the high levels of pyroptotic hepatocyte cell death seen in ACLF.

THU152

Faecal cytokines provide novel insights into the role of gut mucosal inflammation in acute decompensation of cirrhosis

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Background and Aims: Gut dysbiosis increases intestinal inflammation and loss of gut barrier integrity (GBI) in chronic liver disease (CLD). Gut barrier dysfunction enables pathological bacterial translocation (BT), which contributes to cirrhosis-associated immune dysfunction and heightened susceptibility to infection. Little is known about gut-specific inflammation in CLD, and how this differs in patients with acutely decompensated (AD) cirrhosis. Intestinal inflammation is challenging to study in cirrhosis, with difficulty in obtaining representative tissue. We therefore developed a novel approach to characterise intestinal immunopathology by quantifying faecal cytokines (FC) and GBI markers.

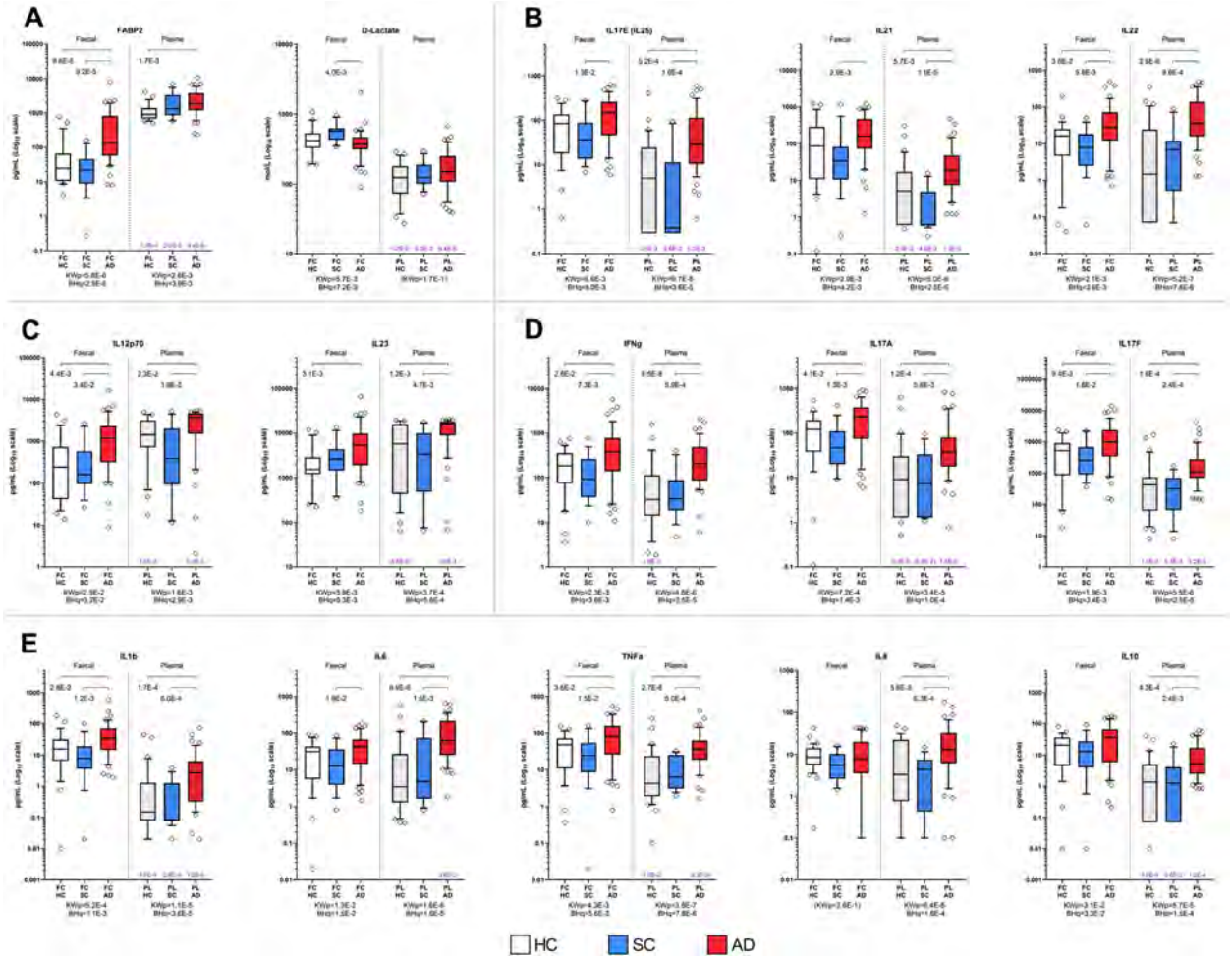

Figure: (abstract: THU152)

Method: Paired faeces and plasma were obtained from 16 patients with stable cirrhosis (SC), 47 AD, and 31 healthy controls (HC). A panel of 15 cytokines and GBI markers including intestinal fatty acid-binding protein-2 (FABP2) and D-lactate were quantified by electrochemiluminescence or ELISA. Correlations between analytes and clinical metadata with univariate and multivariate analyses were performed.
Results: Median ages and MELD scores of AD vs SC patients were 61 (53–68) vs 55 (44–59) years and 18 (13–26) vs 8 (7.0–8.5), respectively. Male gender predominated (AD: 65%; SC: 75%). The causes of cirrhosis were mainly alcohol, non-alcohol-related fatty liver disease and treated hepatitis C. Faecal (F) IL1β, IFNγ, TNFα, IL21, IL17A/F and IL22 were significantly elevated in AD vs SC ($q < 0.01$). F-IL23 was significantly elevated in AD vs HC ($p = 0.0007$). FABP2/D-lactate were significantly increased in faeces in AD vs SC and AD vs HC ($p < 0.0001$) and in plasma ($p = 0.0004$; $p = 0.011$). F-FABP2 correlated most strongly with disease severity (Spearman's rho: Child-Pugh 0.466, $p < 0.0001$; MELD 0.488, $p < 0.0001$). With the exception of IL-8, IL-12 & IL-23, faecal cytokines and F-GBI markers were more discriminant than circulating equivalent molecules in discriminating AD from SC by Principal Component Analysis.
Conclusion: FC-profiling represents a novel approach to the localised measurement of the intestinal cytokine milieu in CLD, and in conjunction with F-D-lactate, with progression to AD from SC being an intestinally initiated and mediated process. These data reveal that AD is characterized by a highly inflamed, permeable gut, and FC profiles are very different from the classical features of systemic inflammation, as assessed by plasma measurements. This is in keeping with skewing T-cell priming towards non-specific upregulation of Th1/17 effector cytokines, and those known to be mediators of gut barrier damage. In AD this perpetuates loss of gut barrier integrity, impairs mucosal healing and propagates BT and systemic inflammation. These data provide insights into intestinal mucosal injury and GBI, as a novel pathobiology in AD.

THU153

Hypofibrinolysis as a contributing mechanism of cirrhotic portal vein thrombosis as evidenced by rotational thromboelastometry (ROTEM)

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Background and Aims: Portal vein thrombosis (PVT) is a well recognized complication of liver cirrhosis. The etiology is thought to be related to a combination of venous stasis from portal hypertension and altered hemostasis from reduced hepatic synthesis of both pro- and anti-coagulant proteins. Rotational thromboelastometry (ROTEM) is a viscoelastic method for investigating the interaction between coagulation factors, platelets, fibrinogen, and fibrinolysis of whole blood. There is a paucity of data examining the ROTEM assay profile of cirrhotic patients with PVT. We hypothesize that cirrhotic patients with PVT will have ROTEM assay profile suggestive of a pro-thrombotic state compared to those without PVT. Thus, the objective of this study was to examine the ROTEM assay profile (i.e. EXTEM Clotting Time [CT], EXTEM Amplitude 10 [A10], FIBTEM, and Maximum Lysis [ML] 30) of cirrhotic patients with PVT compared to those without.
Method: Retrospective study of all patients who received an orthotopic liver transplant at Vancouver General Hospital between Nov 2016 – Oct 2019. ROTEM values were obtained prior to surgical incision liver transplant. Exclusions: Non-cirrhotic patients, anti-platelet or vitamin K antagonists within 5 days of transplant, direct oral anticoagulant within 48 hours, low molecular weight heparin within 24 hours of transplant, heparin before 6 hours of transplant, and those who received frozen plasma immediately before transplant. Chi-square and two tail t-tests (where appropriate) were used to determine statistical significance with $p < 0.05$.
Results: 214 patients were identified with 28 patients excluded based on above criteria. Of the 186 patients remaining, there was no statistically significant difference between gender, mean age, MELD, INR, bilirubin, albumin, platelets, presence of HCC, ascites, hepatic encephalopathy, variceal bleeding, and CKD. Those with PVT had statistically lower ML30 compared to those without. No other significant differences in other ROTEM assays were observed (Table 1).

Table 1: ROTEM assay profile of cirrhotic patients with PVT vs. non-PVT

	PVT (n = 12)	Non-PVT (n = 174)	p-value
EXTEM CT	87.2	83.6	0.88
EXTEM A10	38.8	38.9	0.98
FIBTEM	10.7	11.1	0.83
ML30	2.9	5.8	**0.023**

Conclusion: To our knowledge, this is the first reported study using ROTEM to demonstrate a reduction in the degree of fibrinolysis (ML30) amongst cirrhotic patients with PVT compared to those without. This suggests that hypofibrinolysis may play a mechanistic role in the development of PVT in patients with cirrhosis. Interestingly, there was no difference in other parameters suggesting that coagulation factors, platelets, and fibrinogen function may not play a significant role in its pathogenesis. Further larger prospective studies are warranted to examine the association between ROTEM assay profiles and the development of PVT in cirrhotic patients.

THU154

Lecithin-cholesterol acyltransferase deficiency as an explanatory mechanism for both relative adrenal insufficiency and spur cell anemia in cirrhosis

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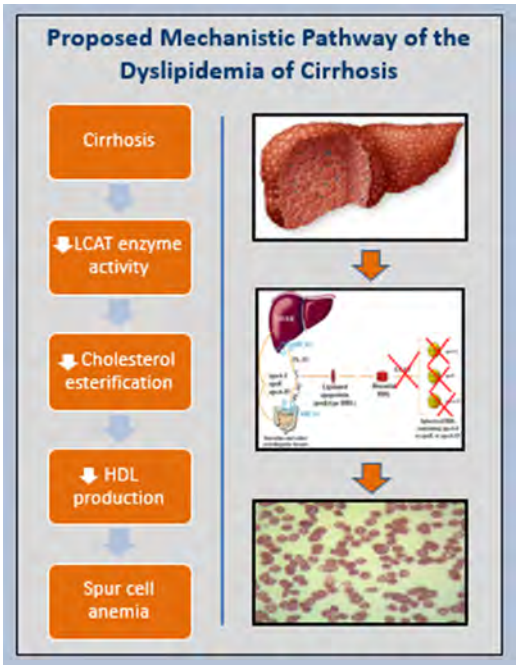
Background and Aims: Lecithin-cholesterol acyltransferase (LCAT) is a key hepatic enzyme responsible for the esterification of cholesterol and formation of high-density lipoprotein (HDL) molecules. However, in cirrhosis, its production wanes with synthetic dysfunction. Similarly, relative adrenal insufficiency (RAI) and spur cell anemia (SCA) are established sequelae of decompensated cirrhosis. As prior research has linked these findings to an underlying dyslipidemic state, we investigated whether LCAT deficiency could be an explanatory mechanism for their development.
Method: 100 hospitalized, non-critically patients with cirrhosis were prospectively enrolled at our academic liver transplantation center between January 2018 and March 2019. Serum HDL levels and percentage of esterified cholesterol (%CE) were measured, peripheral blood smears were obtained, and a high-dose adrenocorticotropin stimulation test was administered. LCAT deficiency was defined as %CE <60, RAI was defined as an increase in total cortisol level <9 µg/dL, and severe SCA was defined as the presence of ≥ 5% spur cells per high-powered-field. The comparable prevalence of these variables with respect to the severity of chronic liver disease was assessed as the primary outcome of interest. Mortality and transplant-free survival (TFS) were important secondary outcomes.

Results: Child-Pugh (CP) distribution of patients was: A-4, B-52, C-44. Mean MELD-Na was 20 ± 7, HDL was 23 ± 13 mg/dL, and %CE was 63% (21% were LCAT deficient). A third of patients had SCA, with nearly half having the severe phenotype. The prevalence of RAI was 39%; 6-month mortality was 22% and TFS was 47%. Compared to CP-B patients, CP-C patients had lower HDL levels (16 vs. 29 mg/dL, p < 0.001) and increased prevalence of RAI (57% vs. 25%, p = .002) and SCA (50% vs. 20%, p = .002). LCAT deficiency was more prevalent in CP-C patients (48% vs. 4%, p < 0.001) and TFS was worse in CP-C patients (25% vs. 64%, p < 0.001). MELD-Na (HR 1.11, p < 0.001) and RAI were found to be independent predictors of mortality (HR 2.12, p = .030).



Conclusion: Concurrent findings of low HDL levels, decreased circulating cholesterol esters, SCA and the presence of RAI all suggest an underlying deficiency of the LCAT enzyme. This constellation of findings is associated with poor outcomes in the absence of transplantation, with RAI being an independent predictor of mortality.

Acute liver failure and drug induced liver injury

THU155

Plasma perfusion combined with plasma exchange improved survival in chronic hepatitis B related acute-on-chronic liver failure patients

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Background and Aims: Artificial liver support systems (ALSS) have been shown to significantly reduce mortality in patients with acute-on-chronic liver failure (ACLF). However, characteristics of patients who would benefit most from ALSS treatment are poorly understood. This study aimed to delineate the indicators for ALSS and evaluate the effectiveness of plasma perfusion combined with plasma exchange (PP+PE) in patients with hepatitis B virus-related ACLF (HBV-ACLF).

Method: A total of 898 patients with HBV-ACLF in a single center were enrolled retrospectively. Propensity score matching (PSM) was used in case-paired analysis. Hepatic or extra-hepatic organ failures were defined by Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) criteria. Complications included ascites, infection, hepatopulmonary syndrome, hepatorenal syndrome, hepatic encephalopathy and upper gastrointestinal bleeding. Numbers of organ failures or complications were used for risk stratification.
Results: Among all patients, 418 patients received standard medical therapy (SMT) and 480 received PP+PE plus SMT. After one-to-one paired PSM, 293 pairs were enrolled. The PP+PE group showed a significantly lower 28-day transplant-free mortality (TFM) than the SMT group. Furthermore, the PP+PE group displayed a significantly higher cumulative survival rate (CSR) in both 28- and 90-day observation durations. When stratified, patients with two or more organ failures or complications from the PP+PE group showed all observed benefits including significantly lower 28- and 90-day TFM and higher CSR. Moreover, PP+PE treatment significantly increased the resolution of organ failures and complications and ameliorated the development of new organ failures and complications.
Conclusion: PP+PE treatment significantly reversed organ failures and ameliorated the development of new organ failures and complications, thus improving the survival of patients with HBV-ACLF, with superior benefits in patients with two or more organ failures or complications.

THU156

The role of urea on the prognosis of severe acute liver injury and acute liver failure

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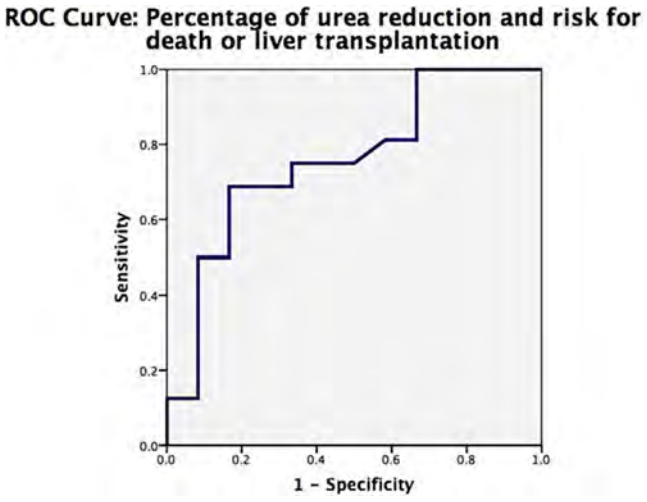
Background and Aims: Acute liver injury (ALI) and failure (AFL) represent a continuum of acute liver disease. Current prognostic models are suboptimal in selecting patients for urgent liver transplantation. Urea synthesis is an essential metabolic liver function through ammonia catabolism in the Krebs-Henseleit cycle. It is influenced by protein-diet, liver and renal function. Liver dysfunction associates with decreased activity of urea metabolism enzymes. We aimed to evaluate a possible association between urea kinetics and outcomes in severe ALI/ALF.
Method: 46 adult patients with severe ALI and ALF were evaluated in a retrospective case-control study, admitted to an intensive care unit (ICU) between 2005 and 2018. However, 17 patients were excluded due to acute kidney injury (AKI) or chronic kidney disease (CKD). The primary endpoint was to evaluate the effect and extension of urea kinetics on patients' prognosis defined by "alive" or "death or liver transplanted (LT)."
Results: 29 patients, 18 females (62%), with mean age 43 ± 15 years were included. ALF developed in 62% of the cases. 9 patients were LT (31%) and 7 died (24%) during their hospitalization. The causes of severe ALI and ALF were undetermined (28%), drug-induced liver injury (24%), primarily caused by acetaminophen and anti-tuberculosis agents, viral hepatitis (17%), autoimmune hepatitis (14%), ischemia (10%) and *Amanita phaloides* poisoning (7%). The outcome LT or death was associated with presence and severity of encephalopathy, respiratory failure, serum levels of albumin, INR, factors V and VII, fibrinogen, glucose, phosphorus, and percentage of urea reduction up to the first 5 days after admission. The only independent factors were severity of encephalopathy and phosphorus. Up to 1/4 of patients without encephalopathy died or required LT. The performance of the percentage of urea reduction for discriminating the outcome LT or death was: AUROC 0.76 [0.57–0.94], p = 0.022. A

decrease of > = 30.6% in urea had sensitivity 75%, specificity 67%, positive and negative predictive value 71% and 67%.



Conclusion: This pilot study suggests that urea kinetics might have a potential role as a biomarker for adverse outcomes in patients with severe ALI and ALF. These results encourage further research with multicenter studies controlled for factors that influence urea production such as diet protein content and muscular mass.

THU157

Idiosyncratic drug-induced liver injury in the elderly: an analysis of cases from the Spanish DILI registry

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Background and Aims: As the life expectancy increases worldwide, it is likely that more elderly will suffer from drug-induced liver injury (DILI). Our aim was to study the influence of subgroups of older age (≥ 65 years) on the phenotypic presentation of DILI, the severity and the causative agents.

Method: We examined 882 cases of idiosyncratic DILI from the Spanish DILI registry. Cases were classified by age into four groups: "young" (<65 years; n = 589); "young-old" (65–74 years; n = 169); "middle-old" (75–84 years; n = 108); and "oldest-old" (≥ 85 years of age; n = 16). We compared patient and DILI characteristics, and analysed the causative agents.

Results: The proportion of females decreased from 50% in the young to 43% in the middle-old (p = 0.018), yet in the oldest-old there was a distinct female predominance (75%; p = 0.011). The mean BMI (±SD) in kg/m^2 significantly increased from 25 ± 3.8 in the young to 27 ± 3.8 in both the young-old and the middle-old, while there was no difference with the oldest-old (26 ± 4.8). All elderly age groups had a significantly higher Charlson comorbidity score than the young patients. Non-liver related death was also more common in the elderly age groups (p = 0.048). Both the time to DILI onset and the time to resolution were not different between the age groups. Jaundice was significantly more common in the elderly (63% in the young vs. 84% in the middle-old and 88% in the oldest-old) and DILI was frequently judged as "severe" in the oldest-old (25% vs. 7% in the young; p = 0.029). There was a clear trend towards more cholestatic DILI cases with increasing age: 14% in the young, 26% in both the young-old and middle-old and 50% of cases in the oldest-old was cholestatic DILI, p < 0.001. This trend remained similar when excluding amoxicillin-clavulanate cases and was also reflected in the alkaline phosphatase values, which were significantly higher in the oldest-old compared to both the young and young-old. Anti-infectives were the most common causative agents in all age groups, followed by cardiovascular drugs in the young- and middle-old and central nervous system drugs in the oldest-old.

Conclusion: Elderly patients with DILI have a higher comorbidity burden and non-liver related mortality compared to the young. The phenotypic presentation of DILI in the oldest-old was different compared to the young- and middle-old age groups with a large proportion of cholestatic DILI cases. As this group will be increasing in the coming years this is an important finding for both clinical practice and industry.

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THU158

Use of the molecular adsorbent recirculating system in acute liver failure: a North American multicenter experience

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Background and Aims: Acute liver failure (ALF) is a rare condition associated with significant mortality. The molecular adsorbent recirculating system (MARS) removes water-soluble and albumin-bound toxins, and aims to allow for native hepatic recovery/sustain ALF patients until a suitable donor organ becomes available for transplant. The role of MARS in transplant-free survival remains in question. This study aimed to evaluate the use of MARS therapy at 3 large North American centres.

Method: Retrospective case series of all ALF patients receiving MARS therapy between January 2009 and January 2019 at the University of Alberta, University of Kansas, and Emory University. Primary outcome was survival to hospital discharge. Secondary outcomes included change in hemodynamic and biochemical parameters post-MARS treatment.

Results: One-hundred four ALF patients (median age 38 [26.5–50.5]; 62.5% female) were treated with MARS (median 3.0 [2.0–6.0] runs; median total duration 24.0 [9.0–33.1] hours), with acetaminophen (APAP) representing the most common etiology (49.0%). Following MARS therapy, APAP patients displayed decreased heart rate (−8.43 [−5.14, −1.72] bpm; p = 0.015) and increased mean arterial pressure (MAP; +8.79 [2.81, 14.78] mmHg; p = 0.005) with no change in vasopressor dosing. No significant change was observed in non-APAP patient hemodynamics. Among APAP patients, ammonia (−50.82 [−74.92, −26.72] mmol/L; p = 0.0001), creatinine (−72.73 [−98.42, −47.06] μmol/L; p < 0.0001), INR (−1.98 [−2.81, −1.15]; p < 0.0001), and lactate (−2.69 [0.4.21, −1.18] mmol/L; p = 0.0008) decreased following MARS, while bilirubin remained unchanged. Post-MARS, non-APAP patients displayed increased MELD score (+5.79 [2.93, 8.59]; p = 0.0002), while no change was observed in APAP patients. Overall, 24 patients underwent orthotopic LT (APAP: 5/51 (9.8%); non-APAP 19/53 (35.8%)). Seventy-five patients (72.1%) survived to 21 days (LT: 22/24 (91.7%); No LT: 53/80 (66.3%)), with 54 patients (51.9%) surviving to 21 days without LT (APAP: 31/51 (60.8%); Non- APAP: 23/53 (43.4%)).

Conclusion: The use of MARS improved the biochemical profile of in ALF patients and, in cases of APAP ALF, improves hemodynamics. A

Variable	APAP (N=51)		Non-APAP (N=53)	
	Change Post- vs. Pre-MARS (95% CI)	P-value	Change Post- vs. Pre-MARS (95% CI)	P-value
Heart Rate (beats/minute)	-8.43 (-15.14 to -1.72)	0.015	-1.81 (-7.45 to +3.83)	0.522
MAP (mmHg)	+8.79 (+2.81 to +14.78)	0.005	-3.06 (-10.25 to +4.14	0.398
Norepinephrine (mcg/kg/min)	-0.021 (-0.60 to +0.017)	0.269	+0.101 (+0.0002 to +0.108)	0.050
Epinephrine (mcg/kg/min)	+0.058 (-0.009 to +0.124)	0.089	+0.029 (-0.269 to +0.084)	0.305
Platelet Count (x10^9/L)	-41.65 (-57.64 to -25.65)	<0.0001	-41.06 (-53.80 to -28.32)	<0.0001
INR	-1.98 (-2.81 to -1.15)	<0.0001	-0.12 (-0.94 to +0.70)	0.768
Total Bilirubin (µmol/L)	+12.29 (-3.85 to +28.43)	0.132	-64.86 (-109.78 to -19.95)	0.006
Ammonia (mmol/L)	-50.82 (-74.92 to -26.72)	0.0001	-24.82 (-48.74 to -0.89)	0.043
Creatinine (µmol/L)	-72.73 (-98.42 to -47.06)	<0.0001	-70.86 (-101.13 to -40.60)	<0.0001
Lactate (mmol/L)	-2.69 (-4.21 to -1.18)	0.0008	+0.58 (-0.87 to +2.02)	0.424
SOFA Score	+2.28 (+1.25 to +3.31)	<0.0001	+3.04 (+1.85 to +4.23)	<0.0001
MELD Score	-0.16 (-2.58 to +2.26)	0.897	+5.76 (+2.93 to +8.59)	0.0002

Figure: (abstract: THU158): Changes in hemodynamic/biochemical parameters post-MARS, stratified by acute liver failure etiology.

larger controlled study is required to evaluate any potential survival advantage (currently ongoing).

THU159

MELD score is the best predictor for transplant-free survival in patients with acute liver injury

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Background and Aims: The management of patients with acute liver injury (ALI) requires precise selection of patients who will likely die without urgent liver transplantation. The differentiation between ALI and acute liver failure (ALF) is hampered by very subtle signs of encephalopathy in acute disease. We aimed to compare the value of ALF early dynamic (ALFED) model, King's College criteria (KCC) and MELD score to predict poor prognosis (death or liver transplantation) in patients with severe ALI.

Method: A retrospective study was conducted on adult patients with severe ALI admitted to an intensive care unit, between 2005 and 2018. Patients were grouped according to their outcome as "alive" or "death or liver transplanted (LT)." The ability of the scores KCC, ALFED and MELD to predict adverse outcomes were evaluated.

Results: Forty-six patients with ALI, 26 female (56%), with mean age 46 ± 17 years were included. ALF developed in 32 patients (70%). Ten patients were LT (22%) and 17 died (37%) during their hospital stay. Causes of ALI were: drug-induced liver injury in 12 (26%), 3 of which acetaminophen related; viral hepatitis in 7 (15%), ischemic hepatitis in 6 (13%), *Amanita phaloides* poisoning in 5 (11%), and undetermined in 10 (22%). Invasive mechanical ventilation (VMI), vasopressors and renal replacement therapy were required in 11 (30%), 13 (28%), and 8 (17%) patients, respectively. The outcome LT or death associated with liver failure and severity of encephalopathy, higher age, INR, factor V, fibrinogen, albumin and creatinine serum levels, cardiovascular shock and respiratory failure, as well KCC and MELD, but not ALFED. Up to 1/3 of patients without encephalopathy died or required LT. MELD>29 was the only independent risk factor (OR 35.7 [3.5–368.8]). The performances of the different scores for discriminating the outcome LT or death were: MELD>29 AUROC 0.83 [0.68–0.99], p = 0.001, sensitivity (Se) 85%, specificity (Sp) 75%, positive predictive value (VPP) 85% and negative predictive value (NPV) 21%; KCC AUROC 0.75 [0.57–0.92], p = 0.020, Se 67%, Sp 79%, PPV 82% and NPP 37%; ALFED AUROC 0.62 [0.42–0.82], p = 0.244, Se 31%, Sp 93%, PPV 83% and NPV 56%. MELD>29 was superior than other scores even in patients with definitive ALF.

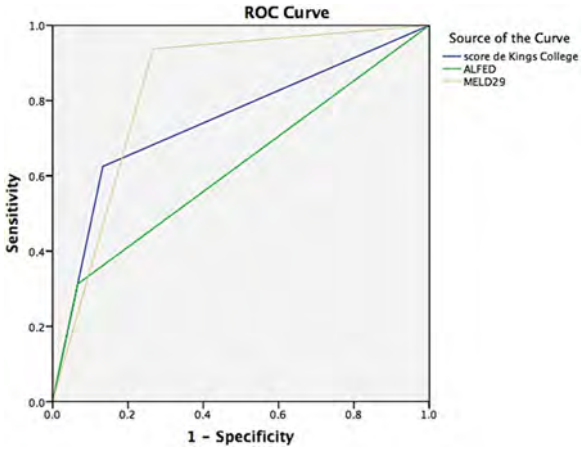

Figure: ROC Curve: Performances of the different scores for discriminating the outcome.

Conclusion: MELD score is superior to KCC and ALFED scores in predicting death or LT in severe ALI patients. MELD>29 accuracy is independent of the presence of encephalopathy. ALFED score has, however, an excellent Se and PPV.

THU160

Ketamine for maintenance sedation in critically ill burned patients is associated with liver dysfunction and acute kidney injury

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Background and Aims: Intravenous ketamine is given for maintenance sedation of critically ill burned patients. Ketamine has been associated with drug-induced liver injury (DILI), including cholangiopathy. Cholestasis has been associated with mortality in critically ill burned patients(1). We investigated the relationship between ketamine exposure and outcomes, including liver dysfunction (LD) and acute kidney injury (AKI), in critically ill burned patients.
Method: We conducted a retrospective, single-center cohort study among consecutive patients admitted for burn injury in our burn intensive care unit (BICU) between December 2014 and December 2018. We included only patients admitted within the 3 first days following the burn injury and with a BICU stay ≥ 10 days. Drug exposure was defined as the total amount of drug received during the BICU stay divided by the numbers of days of exposure. Exposition to midazolam, a drug without any reported DILI, used as an alternative to ketamine for sedation, served as control. Primary endpoint was LD defined by total bilirubin ≥ 2 upper limits of normal (ULN). Continuous variables were expressed as medians with interquartile ranges (IQRs). We used cox models adjusted for severity of illness to measure the associations between ketamine exposure, LD, and KDIGO-defined AKI.
Results: A total of 307 patients were included LD was observed in 46 (15%) patients and was associated with severity of illness at admission, including burned body surface area ($p < 0.001$), Abbreviated Burn Severity Index ($p < 0.001$), Simplified Acute Physiology Score II ($p < 0.001$). Ketamine and midazolam exposure were also higher in patients with LD compare to patients without LD: respectively 312 mg/d [40–1139] vs 20 mg/d [0–68,8], ($p < 0,001$) and 95 mg/d [36–156] vs 0 mg/d [0–64], ($p < 0,001$). Adjusted for severity of illness, ketamine exposure was still associated with liver dysfunction and not midazolam (Figure 1). Ketamine, and not midazolam, was associated [adjusted hazard ratio (95% confidence interval) of 1.6 (1.1, 2,4), ($p = 0,018$)] with AKI only in the subgroup of patients with liver dysfunction.
Conclusion: In this cohort of critically ill burned patients, a population at high risk of liver dysfunction and exposed to a large amount of ketamine for sedation maintenance, Ketamine appears as a risk factor of liver dysfunction and may account for other organ failures, including AKI.

THU161

The therapeutic role of iNOS-expressed myeloid derived suppressor cells in acetaminophen induced acute liver failure

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Background and Aims: An overdose of acetaminophen (N-acetyl-p-aminophenol or APAP) is one of major causes of acute liver failure. The toxic metabolites of APAP induce hepatocyte necrosis and activate the inflammatory responses to exacerbate liver injury. Myeloid-derived suppressor cells (MDSCs) increase in inflammatory diseases to regulate immune responses and are proposed to be used as adoptive immune cell therapy. Our aim is to investigate the therapeutic role of MDSC in APAP-induced acute liver failure.
Method: The BLAB/c mice were injected with a sublethal/lethal dose of APAP as the murine model. The MDSCs were defined as $CD11b^+Gr\text{-}1^+$ cells with suppressive ability on $CD8^+$ T cell proliferation. iNOS knockout mice were also used to investigate the role of iNOS in the protection functions of MDSC.

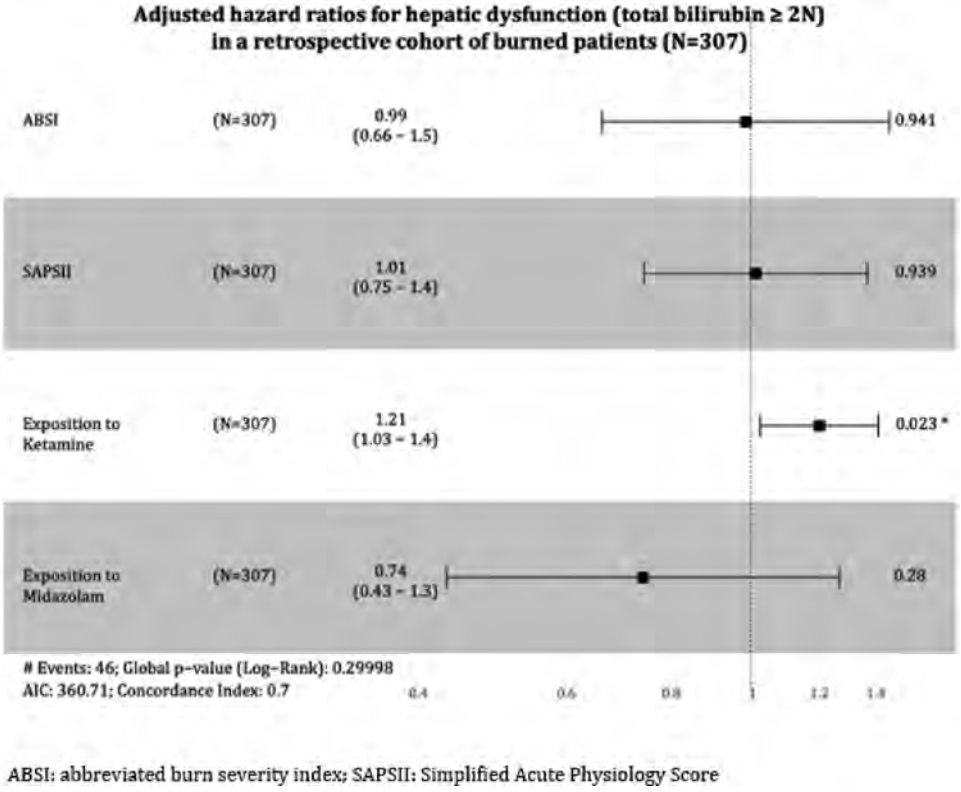

Figure: (abstract: THU160)

Results: A sublethal challenge of APAP could cause the intra-hepatic MDSCs accumulation and protect mice from subsequent lethal challenge of liver injury induced by APAP. This protection was lost if MDSC was depleted, and inducible nitric oxide synthase (iNOS) was the key molecule in this MDSC-mediated protection. Taking advantage of these observations, different bone marrow-derived MDSCs (BM-MDSCs) were generated and the TNF-α/LPS-primed BM-MDSCs had dominant iNOS expression and with the strongest liver protection ability after adoptive transfer of these BM-MDSCs into mice with APAP-induced acute liver failure. Similarly, iNOS was the key molecule for protection functions of these TNF-α/LPS-primed BM-MDSCs and induced a decrease influx of intrahepatic neutrophil infiltration that explained the therapeutic role of these MDSCs.
Conclusion: We demonstrated the protective role of MDSCs and therapeutic effect of *in vitro*-generated BM-MDSCs in APAP-induced liver failure. This protection is mediated by iNOS. Moreover, we also generated MDSCs from human peripheral blood mononuclear cells (PBMCs) with similar phenotype. These findings suggest the potential role of MDSCs as a cell-based therapy for APAP-induced liver failure.

THU162

Prevalence, incidence, and characteristics of hepatorenal syndrome-related acute kidney injury in the United States

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Background and Aims: Hepatorenal syndrome (HRS) type 1 is a severe form of acute renal failure that is common in patients (pts) with decompensated cirrhosis (DC). In 2015, the International Ascites Club (IAC) newly defined HRS as a subset of acute kidney injury (AKI) to enable early identification based on dynamic changes of serum creatinine (sCr), and expected better outcome with earlier therapy. We assessed the prevalence and incidence of HRS-AKI stages 2 and 3 and HRS type 1 as well as the practicability of the new IAC 2015 criteria.
Method: HRS was identified among hospitalized pts (≥ 18 years) with DC in 1/1/14 – 12/31/17 from a large United States (US) electronic medical record database (Explorys). HRS-AKI stages 2 and 3 and HRS type 1 were defined according to IAC 2015 and ICA 2005 criteria.
Results: Prevalence and incidence of HRS-AKI and HRS type 1 were assessed in 2017 with a starting population of 12,207 pts with DC. Of these, pts with hospitalization in 2017, sCr at baseline and during hospitalization, continuous activity in the database in 2016–2017, and no prior diagnosis of HRS-AKI or HRS type 1 (incidence assessment only) were selected. In hospitalized DC pts, the 2017 prevalence of HRS type 1 was 6.2% (70/1,135) and the incidence was 5.7% (62/1,083). By contrast, 33% higher prevalence (8.3%; 94/1,135) and incidence (7.6%; 79/1037) rates were found using the new HRS-AKI criteria. To characterize HRS-AKI pts, 552 pts who met the study criteria were identified from a starting population of 42,322 pts with DC in 2014–2017. Of these, 74.6% and 25.4% had stage 2 and stage 3 AKI, respectively. Mean (± standard deviation [SD]) baseline sCr values were 1.0 ± 0.6 and 0.9 ± 0.6 mg/dL in stage 2 and 3, respectively, and increased to 2.4 ± 1.5 and 5.2 ± 8.2 mg/dl, respectively, at hospitalization. Mean age was 60 years and 57.4% were male. Race was 74.5% Caucasian and 9.6% African American. Most frequent liver diseases assessed were chronic hepatitis C (23.9%), alcoholic hepatitis (9.6%), and non-alcoholic fatty liver disease (13%). Other top comorbidities were hypertension (54%), diabetes (31.7%), chronic obstructive lung disease (20.3%), and chronic kidney disease (19%).
Conclusion: The new HRS-AKI criteria can be easily applied to the US population because baseline sCr values important for the diagnosis and treatment of HRS-AKI are available. This will lead to diagnosis of more pts as expected and could facilitate earlier therapy.

THU163

Bioenergetics defect of CD14+ monocytes are associated with increased mortality in acute liver failure

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Background and Aims: Increase systemic inflammatory response as a result of massive hepatic injury is associated with development infections & high mortality in ALF though the mechanisms are unclear. We investigated the underlying cellular mechanisms for increased susceptibility to infection & high mortality in ALF
Method: A panel 31 cytokines & growth factor were analysed in ALF (N = 30). Distribution of hepatic macrophages (ALF, N = 10, Healthy (H) = 10), monocytes (ALF N = 15; H = 15) & their phagocytosis was studied by FACS. Mitochondrial respiration and glycolysis were analysed in shorted CD14+monocyte (ALF N = 18, H = 10) by Agilent–XFe24–analyzer. Expression of Glycolysis and TCA pathway gene were done by qPCR.

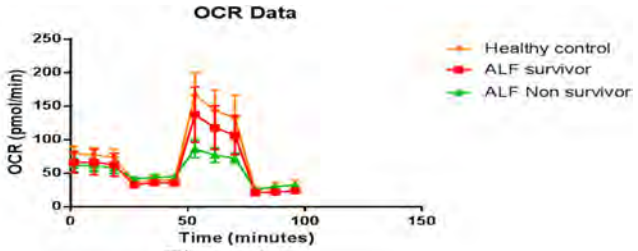

Figure A

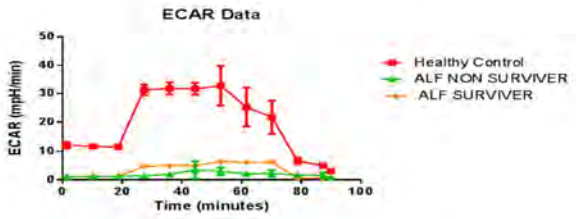

Figure B

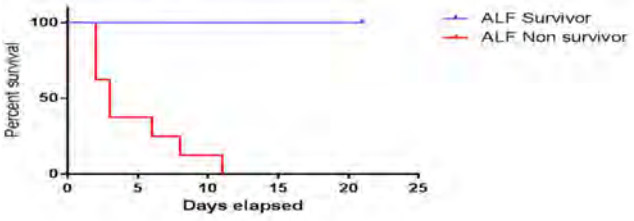

Figure C

Results: 21of 30 ALF patients died or went for liver transplant (non–survivor) and 9 patients showed spontaneous recovery (survivor). Cytokine showed reduction of innate immunity–related cytokines (MCP-3,IL-1β,IL-6,IL-10,& IL-17) in ALF non-survivors. CD68+macrophage while increased in ALF liver ($p = 0.004$),were deficient in phagocytosis($p = 0.001$) in comparison to healthy. Similarly,the CD14 +monocytes in ALF non-surviver showed reduction ($p = 0.001$) & phagocytosis ($p < 0.001$) in comparison to survivors, suggesting the

failure of mono-mac system in ALF non surviver. In comparison to healthy monocyte, the ALF monocyte showed significant decrease in mitochondrial respiration (Fig. 1A),glycolysis (fig. 1B) & showed decrease expression of enzyme associated with ATP production in glycolysis (PGK1) & TCA cycle (IDH,OGDH) in ALF non surviver, suggesting Bioenergetic failure in ALF. Further analysis of mitochondrial-respiration of monocyte in living-donor-liver-transplant donor before & after surgical resection at D3&D7 showed significant decrease in mitochondrial-respiration at D3 which recover at D7 with increase in liver mass. these data suggest the loss of hepatic mass adversely affects the energy metabolism of monocytes. In 21Ds of follow-up while9 patients discharged form ICU & survived 9 died or went for liver transplant. Baseline mitochondrial respiration of monocyte ($p < 0.001$; AUROC = 1) predict the early mortality (21 Ds) in ALF, ALF with OCR less then = 21 pM/min showed increase in mortality (Fig. 1C).

Conclusion: Broad defect in energy metabolism in ALF, lead to a compromise of mono-mac functions & associated with early mortality. Restoring the energy metabolism of monocytes may prevent the secondary infection & mortality.

THU164

Ferroptosis related regulatory protein NCOA4 and its lncRNA-mRNA co-expression network in patients witn anti-tuberculosis drug-induced liver injury

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Background and Aims: Patients with anti-tuberculosis(anti-TB) drugs induced liver injury(DILI) greatly increased the difficulties of anti-TB treatment. Until now, the pathogenesis of anti-TB related DILI is not very clear. In this study, we aimed to investigate important signaling pathways and related genes in development of the disease and construct profile of lncRNA-mRNA co-expression network to further understand the pathogenesis.

Method: Totally 16 patients with anti-TB related DILI and 16 patients without DILI (as control) were enrolled in this study. Total serum RNA was collected, Affymetrix Human Transcriptome Array 2.0 was applied to detect the differentially expressed genes [fold change ≥ 2.0, $p < 0.05$], as well as variable splicing event [splicing index ≥ 2.0, $p < 0.05$]. The Metascape platform was applied to analysis of differentially expressed mRNAs, and gene interaction matrix was constructed based on Pearson correlation coefficient to explore the non-coding RNA related to the disease. Finally, total RNA was extracted from serum, and the selected important genes were verified by real-time fluorescent quantitative PCR.

Results: Contrast to control group, there were 568 deferentially expressed coding genes, most of which exhibited differential alternative splicing, and 845 non-coding transcripts involved in anti-TB DILI. KEGG enrichment on significantly different mRNAs highlighted the ferroptosis involving in anti-TB DILI that presenting as one of the top 20 signaling pathways, which referred to FTH1(Log FC = 2.05),FTL(Log FC = 2.94),NCOA4(Log FC = 1.65),PCBP1(LogFC = 2.5),PCBP2(Log FC = 2.32) and SAT1 (Log FC = 1.97). Co-expression analysis of mRNAs and ncRNAs showed that NCOA4, which was closely related to FTH1 (correlation P = 0.97) probably involved in the process of anti-TB DILI. In addition, the network suggested that mRNAs related to ferroptosis can be linked to each other by non-coding RNAs, such as FTH1P3(Log FC = 1.27) contemporary connecting to FTH1, FTL and NCOA4($p = 0.97$,0.97 and 0.96, respectively) (Figure 1). Furthermore, RT-PCR results confirmed both expression of NCOA4 and FTH1P3 were significantly higher in anti-tuberculosis patients with DILI than no DILI patients($p < 0.05$).

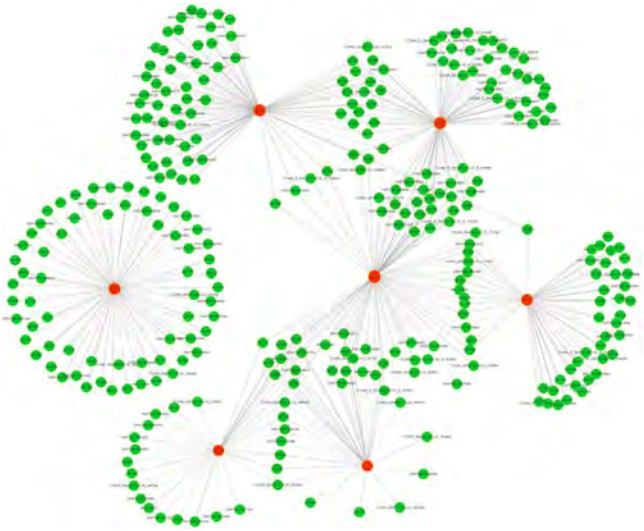

Figure 1: Non-coding RNA co-expressed with seven ferroptosis-related genes, red for ferroptosis-related genes, green for non-coding RNA; solid line for positive correlation, and dashed line for negative correlation.

Conclusion: Patients with anti-TB DILI have obviously altered gene expressions and alternative splicing events compared with the control. NCOA4 acting as a selective cargo receptor for autophagic turnover of ferritin (ferritinophagy) and FTH1P3, have a co-expression relationship with NCOA4 may play an important role in anti-TB DILI, worthy to be further studied.

THU165

AARC score has better accuracy at predicting 90-day mortality in drug induced acute-on-chronic liver failure (DILI - ACLF)

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Background and Aims: Of the various acute insults in Acute on chronic liver failure(ACLF) patients, Drug induced liver injury(DILI) is one of the major culprit. We compared disease severity and outcome in those having Drug induced acute on chronic liver failure versus those having other acute hepatic insults.

Method: Consecutive ACLF patients registered in APASL-ACLF research consortium were included. Demography and outcome of those having Drugs as an acute insult(DILI-ACLF) were compared to rest of other patients (non-DILI ACLF). Predictors of mortality in those having Drug induced liver injury as an acute insult were identified using Cox regression.

Results: Of the Total 3132 patient studied,262(8.4%) had Drugs as an acute insult. Among Drugs, Complementary and Alternative Medicines was major culprit (5.6%) followed by Anti Tubercular drugs(2.8%). Mean age of patients having DILI as an acute insult was 47.35 ± 13.75 years which was comparable to other group 44.22 ± 12.21 years. In 28% of patients having Drugs as an acute insult the underlying chronic insult remain unknown. Baseline MELD (30.5 ± 27.2) was higher in patients of ACLF having DILI as an acute insult as compared with other acute insults (28.86 ± 7.02). Other severity score CTP, SOFA,CLIF-SOFA and AARC score at baseline were comparable among 2 groups. 91.8% of patient having DILI as an acute insult have one or more organ failure at presentation as compared to 86.1% of non-DILI acute insult($p = 0.003$). 30 days mortality (39.7%) was significantly higher in DILI group as compared to other acute insults (28.6%) ($p = 0.004$). Mean survival in DILI-ACLF was 49.99 ± 2.49days which was significantly lower than non DILI ACLF 58.94 ± 0.74 days ($p = 0.005$). MELD Score greater than 30 at baseline predict 90 days mortality with 69.2% sensitivity and 71% specificity whereas AARC

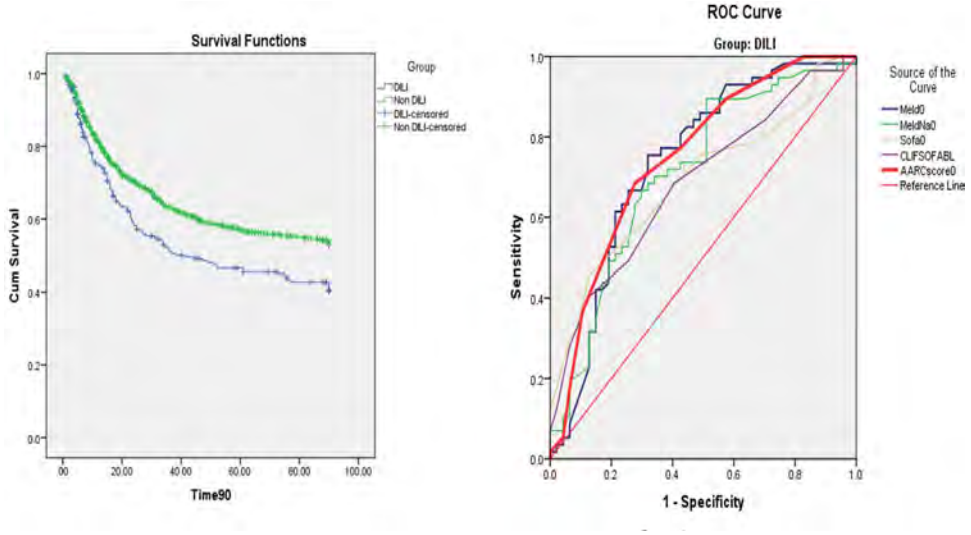

Figure: (abstract: THU165)

score greater than 10.5 predicts 90 days mortality with 68.4% Sensitivity and 73% specificity. ROC comparing MELD,CTP,SOFA, CLIF-SOFA and AARCscore at baseline revealed significantly higher area under curve for AARC score (0.75, $p < 0.001$)

Conclusion: Patients having Drugs as an acute insult in Acute on Chronic Liver Failure have poor outcome as compared to those having other acute insults. Baseline AARC score more than 10.5 has highest AUROC to predict 90 days mortality in DILI-ACLF patients

THU166

Clinical characteristics and prognostic risk factors for patients with hepatic sinusodial obstruction syndrome caused by gynura segetum

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Background and Aims: Hepatic sinusoidal obstruction syndrome (HSOS) induced by Gynura segetum is associated with a notable mortality due to the absence of prompt diagnosis and effective therapy. The risk factors influencing the prognosis have still remained elusive. To describe clinical features and evaluate effects of anticoagulants on survival rate in patients with Gynura segetum-induced HSOS, and identify independent prognostic risk factors as well.
Method: Patients' clinical data, including medical history, symptoms, signs, imaging characteristics, laboratory test results, anticoagulant therapy and outcomes were collected. The prognostic risk factors of HSOS were analyzed by cox regression model.
Results: In this study, 49 patients from 5 hospitals were included, and the median duration of follow-up was 36 months. The main clinical manifestations were ascites (98.0%), abdominal distension (91.8%), hepatomegaly (51.0%), lower limb edema (49.0%), esophageal and gastric varices (42.9%), and splenomegaly (42.9%). The majority of patients had typical map-like or mottle-like radiographic imaging findings. The 1-, 3-, 6-, and 36-month survival rates were 91.8%, 85.7%, 81.6%, and 75.5%, respectively. Anticoagulants were administered to 27 patients (55.1%), and among them, 24 patients (88.9%) survived. The survival rate in anticoagulation group was significantly higher than that of control group (13/22, $\chi^2 = 5.821$, $p = 0.016$). White blood cell count, total serum bilirubin level, and albumin level were the independent prognostic factors of HSOS.

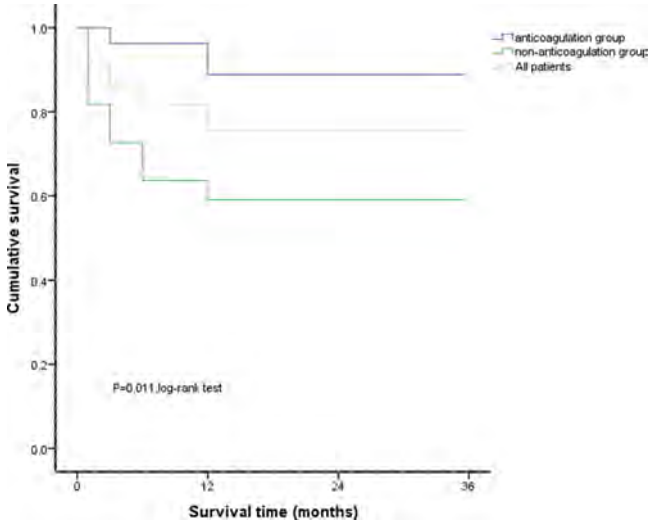

Figure: (abstract: THU166)

Conclusion: White blood cell count, total serum bilirubin level, and albumin level were the independent prognostic factors of HSOS induced by Gynura segetum. Although the mortality rate was high, however, anticoagulation therapy was effective to improve the clinical outcome.

THU167

Umbilical cord-derived mesenchymal stem cells regulate ferroptosis via the activation of NRF2 are signaling pathway for the treatment of acute liver failure

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Background and Aims: Acute liver failure (ALF) is characterized by widespread hepatocyte death and sudden severe liver dysfunction, which can even lead to multi-organ failure and death. However, the manner of hepatocyte death is still not fully clear. Emergency liver

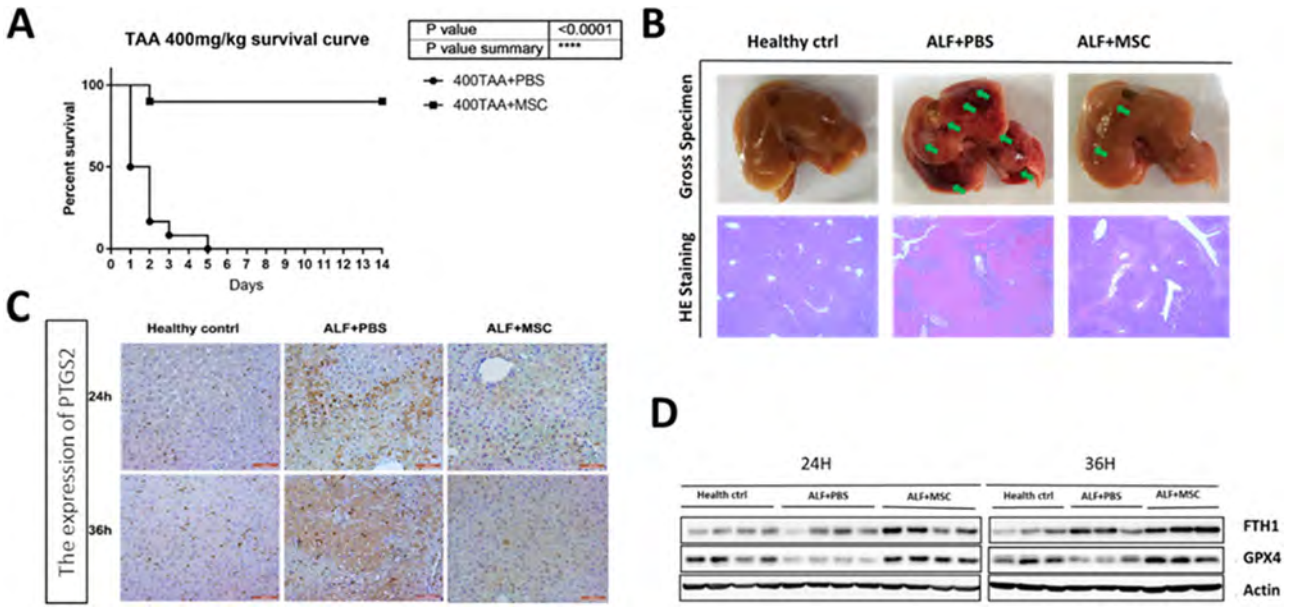

Figure: (abstract: THU167)

transplantation as an optimal treatment for ALF is greatly hampered by the critical shortage of liver grafts. Worse still, the survival rates are inferior to those patients undergoing elective transplantation for chronic liver disease. Therefore, it is urgent to clarify the exact pathogenesis of ALF and develop effective treatments based on it. This study was to investigate the therapeutic effects and possible mechanism of human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) on ALF in murine models.

Method: In the present study, a murine ALF model was established by intraperitoneal injection of thioacetamide (TAA) at lethal dose (at least 400 mg/kg). Human UC-MSCs (2 × 10*6 per mouse) was infused via tail vein to those mice with ALF. Hepatocyte cell line or primary hepatocytes were treated with thioacetamide and RSL3 (Ferroptosis inducer) with or without Liproxstatin-1(Ferroptosis inhibitor) to mimic liver injury and co-cultured with UC-MSCs or MSC conditional medium (UC-MSCs-CM) for in vitro analyses.

Results: Ferroptosis were observed in mice suffering from TAA-induced ALF, including smaller mitochondria with increased mitochondrial membrane density and reduction of mitochondria crista, intracellular iron accumulation, lipid peroxidation with higher ROS level, decreased expression of GPX4 and FTH1, characteristically increased expression of PTGS2 and SLC7A11. This type of cell death is significantly different from other cell death in terms of morphology, genetics and biochemistry. All these pathological changes were revered following a tail venous transfusion of UC-MSCs (2 × 10*6 per mouse). As expected, hUC-MSCs significantly improved liver function and decreased the mortality rate of mice with ALF. To validation, our results showed that the Ferroptosis phenotype induced by thioacetamide and RSL3 can be reversed by Liproxstatin-1 and MSCs. Furthermore, we found that the expression level of P62, Nrf2 and its targeted genes (such as Nqo-1, Txn, Gsr and so on) were upregulated upon MSCs treatment. The rational mechanism could be the accumulation of P62 in cytoplasm and its competitive combination with Keap1, which leaded to more Nrf2 translocate to nucleus and then bind to ARE for transcription of cytoprotective genes.

Conclusion: Our study revealed that UC-MSCs were effective for the treatment of ALF via inhibiting Ferroptosis through the activation of Nrf2-ARE signaling pathway.

THU168

Novel in vivo tracing of the hepatocyte origin of extracellular vesicles in mice with experimental liver disease

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Background and Aims: Most information about hepatocyte-derived exosomes and extracellular vesicles (EVs) and their role in health and disease derives from cell culture experiments, which do not represent the complexity of whole organisms. The lineage reporter mT/mG mouse strain allows the generation of mice that express the Tomato-dye protein in the plasma membrane of all cells except in Cre-recombinase expressing cells, which express the Green Fluorescent Protein (EGFP). Our Aim was to evaluate the lineage reporter mT/mG mouse strain in experimental liver disease as a novel approach for the in vivo identification of circulating EVs according to the cell of origin.

Method: The mT/mG mouse strain (Stock 07676, Jackson Lab) was crossbred with mice expressing Cre-recombinase under the control of the Lysozyme-C (LysMCrexmT/mG mice, EGFP in myeloid-derived cells) or the Albumin promoters (AlbCrexmT/mG mice, EGFP in hepatocytes). Non-fluorescent mice (C57Bl6/J) and the original mT/

mG mouse strain were used as controls. Hepatic damage was induced by acetaminophen administration (APAP, 300 mg/kg bw ip). EVs were isolated by immune-magnetic separation (Mouse Exosome Isolation Kit Pan [CD9, CD63 and CD81 proteins] or GFP Isolation Kit, Miltenyi) from mouse plasma, and by ultracentrifugation of culture media from primary hepatocyte cultures from each mouse strain. EVs were analyzed by flow cytometry (FACS, MACSQuant16), Nanoparticle Tracking Analysis (NTA), Dynamic Light Scattering (DLS), transmission electron microscopy (TEM) and Western Blotting.
Results: The plasma concentration of EGFP-positive EVs was low in Vehicle-treated AlbCrexmT/mG mice but it largely increased in APAP-treated mice, as assessed by FACS. In contrast, APAP treatment did not change the plasma concentration of EGFP-positive EVs in LysMCrexmT/mG mice. EGFP-positivity of EVs from AlbCrexmT/mG mice was confirmed by FACS in plasma and hepatocyte culture media samples, and by Western blotting in exosomes isolated from both sources. In mouse plasma samples, the immune-magnetic isolation of hepatocyte-derived and myeloid cell-derived EGFP-positive EVs was also confirmed by FACS and Western blotting. The characteristics of exosome population were confirmed in all EVs isolates.
Conclusion: The circulating concentration of hepatocyte-derived EVs is low in normal animals, but it considerably increases after acute hepatic insults. The lineage reporter mT/mG mouse strain allows the evaluation and isolation of hepatocyte-derived and myeloid cell-derived EVs in murine models of liver disease. This highly valuable new approach for the in vivo study of the cell-type of origin of EVs overcomes a major limitation in EVs research, being also applicable to fields other than Hepatology.

THU169
Markers of neutrophil extracellular traps are associated with poor outcome in patients with acute liver failure

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Background and Aims: Acute liver failure (ALF) is characterized by significant changes in the hemostatic system and by systemic inflammation. The formation of neutrophil extracellular traps (NETs), in which an activated neutrophil expels its DNA, histones and granular enzymes, to form web-like structures, has been discovered as a new feature of the immune system, and has been associated with immune-mediated - and thrombotic diseases. Intrahepatic NET formation coupled to activation of coagulation has been shown to drive a variety of liver diseases in animal models. In clinical studies, markers for NETs, notably cell-free DNA and the more specific myeloperoxidase (MPO)-DNA, a neutrophil-specific enzyme attached to cell-free DNA, have been indicated to have prognostic utility, but have not been studied in acute liver failure before. We hypothesized that formation of NETs occurs in patients with ALF, and further hypothesized that NETs contribute to progression of disease, promote hemostasis and could have prognostic value in ALF.
Method: A total of 676 patients with ALF (INR >/ = 1.5) or severe acute liver injury (ALI; INR >/ = 2.0) were recruited from the US ALF Study Group Registry between 2011 and 2018, of which 308 patients (45.6%) had acetaminophen-induced ALF. Bleeding occurred in 50 patients (7.4%), and 483 patients (71.4%) survived without liver transplantation. Levels of cell-free DNA and MPO-DNA complexes, were measured using enzyme-linked immunosorbent assays in plasma samples obtained at admission and compared to levels in healthy controls.
Results: Levels of cell-free DNA were 6.8-fold and MPO-DNA complexes 2.5-fold higher in patients with ALF compared to healthy controls. Cell-free DNA levels were not associated with 21-day transplant-free survival, nor with bleeding complications, but were higher in those patients with acetaminophen induced liver failure and in those patients requiring renal replacement therapy. MPO-DNA levels were 30% higher in patients with ALF who died or required urgent liver transplantation. MPO-DNA complex levels were not associated with bleeding complications.
Conclusion: Plasma levels of cell-free DNA and MPO-DNA complexes were significantly elevated in patients with ALF. Levels of MPO-DNA complexes, but not of the much less specific NET marker cell-free DNA, were associated with death or (urgent) liver transplantation, suggesting that increased NET formation might contribute to disease progression and ultimately death.

THU170
Activation ot the aryl hydrocarbon receptor sensitizes to acetaminophen-induced acute liver failure

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Background and Aims: Acetaminophen (APAP)- induced liver damage is one of the most common causes of acute liver failure. However, the risk factors determining hypersensitivity to APAP remain poorly defined. The transcription factor aryl hydrocarbon receptor (AhR), which can be activated by environmental, dietary, microbial and metabolic ligands, is a direct inducer of CYP1A2, one of the major enzymes involved in the generation of toxic APAP metabolites. Therefore, we hypothesized that AhR activation might contribute to APAP-induced hepatotoxicity.
Method: Wildtype or conditional AhR knockout mice lacking AhR in hepatocytes ($Alb^{\Delta/\Delta AhR}$) were subjected to a combined treatment with APAP and the non-toxic gut-derived AhR ligand 2-(1'H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE).
Results: Administration of ITE together with a normally sublethal APAP overdose (350 mg/kg) caused 80% mortality within 8 hours, whereas all vehicle-treated control mice survived ($p = 0.0002$). Accordingly, we found vast necrotic areas in liver tissue ($p < 0.0001$) and strongly elevated serum transaminase levels (ALT: 7616 vs 812 U/L, $p < 0.0001$) in mice, which were co-treated with ITE and APAP, as compared to controls receiving vehicle and APAP. Of note, even at APAP doses equivalent to the recommended therapeutic range in humans, AhR activation by ITE induced substantial liver damage as compared to vehicle treatment (ALT: 1488 vs 117 U/L, $p = 0.0043$). In contrast, $Alb^{\Delta/\Delta AhR}$ mice were largely protected from ITE-induced disease aggravation. Indeed, serum ALT levels (1063 vs 3247 U/L), $p = 0.0012$) were significantly lower as compared to littermate controls. Moreover, TUNEL staining of liver sections revealed greatly reduced hepatocyte death in $Alb^{\Delta/\Delta AhR}$ mice following combined APAP and ITE treatment ($p = 0.007$). Mechanistically, AhR activation by ITE fueled hepatic accumulation of toxic APAP metabolites by up-regulating expression of the APAP-metabolizing enzymes CYP1A2 ($p < 0.0001$) and CYP2E1 ($p = 0.0077$).
Conclusion: AhR activation in hepatocytes induces accumulation of toxic APAP metabolites aggravating APAP hepatotoxicity. Thus, AhR activating ligands, which can originate from various sources, such as nutrition or gut microbiota, might be a risk factor sensitizing to APAP-induced acute liver failure.

THU171

Human bone marrow mesenchymal stem cell's small extract vesicles promote hepatocyte regeneration in acute liver failure

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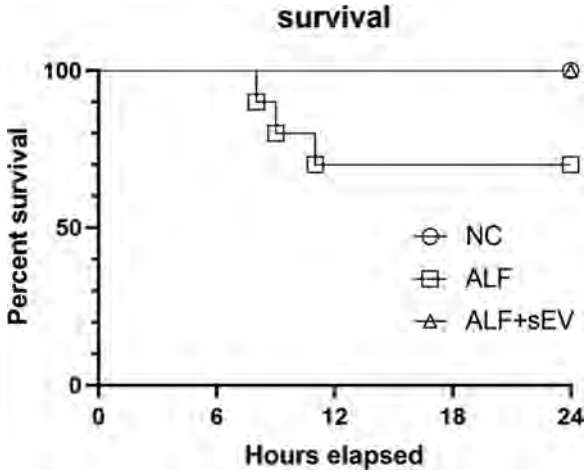
Background and Aims: Acute liver failure (ALF) is a severe, life-threatening syndrome with high mortality due to a shortage of effective agency. How to promote hepatocyte regeneration is the key to rescue ALF. Previous studies have confirmed that mesenchymal stem cells (MSCs) derived small extract vesicles (sEVs) can regulate the proliferation and apoptosis of endogenous cells, but whether it can promote the proliferation and apoptosis of hepatocytes in acute liver failure is unclear.
Method: To establish the ALF cell model of L02 cell line induced by H_2O_2 and ALF mouse model induced by GalN/LPS, collect and identify hBMSC-sEVs, and co-culture with ALF hepatocytes, then detected the proliferation and apoptosis of hepatocytes in ALF cell model by fluorescent labeling technique, meanwhile, detected the hepatocytes activity of by CCK8. Injected hBMSC-sEVs into ALF mouse by tail vein to evaluate the effect on ALF mouse. To test the molecules and genes of proliferation and apoptosis by Western Blotting and qPCR.
Results: The hBMSC-sEVs were fused with ALF cell model, and the activity of hepatocytes in ALF cell model was increased. In vivo tracing showed that hBMSC-sEVs were aggregated in liver of ALF mouse. The levels of ALT, AST and TB reduced, and 24-hour mortality of hBMSC-sEVs infusion mouse was lower than that in the control group, and the liver inflammatory infiltration, hyperemia decreased, meanwhile, hepatocyte proliferation increased. hBMSC-sEVs could upregulate pAKT and pSer9-GSK3 β, CCND1 and Bcl-2 expression increased, and p53, Bax and cMyc expression decreased.



Conclusion: hBMSC-sEVs can improve the prognosis of acute liver failure by promoting hepatocyte proliferation and reducing apoptosis in vitro and in vivo.

THU172

Cut-off level of serum cytokeratin 18 for diagnosis of acute-on-chronic liver failure in chronic hepatitis C cirrhosis

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Background and Aims: Acute on chronic liver failure (ACLF) is a new form of liver failure that has unacceptable high rates of mortality. There is evidence of hepatocyte cell death in ACLF either by necrosis or apoptosis. The caspase-cleaved cytokeratin18 fragments (M30) is a marker of caspase-mediated apoptosis. The aim is to evaluate the value of serum cytokeratin 18 level in diagnosis of ACLF in chronic HCV cirrhotic patients and its correlation with ACLF severity.
Method: This study included 60 chronic HCV cirrhotic patients with ACLF (Group 1), 15 chronic HCV compensated cirrhotic patients (Group 2), and 15 healthy controls (Group 3). Laboratory investigations and radiological examination with calculation of CTP, MELD, CLIF-OF (CLIF Consortium Organ Failure Score) and calculation of CLIF-C ACLF score using EASL CLIF ACLF calculator, were done for all enrolled individuals. Serum level of caspase cleaved CK 18 (M30) using ELISA kits, was measured for all enrolled individuals.
Results: The most common precipitating factor of ACLF was infection which represented 61.7% and the most common infection was SBP (30%). The most common organ failure was renal failure (81.7%). MELD score was significantly higher in Group 1 (32.32 ± 6.76) compared to Group 2 (7.67 ± 2.06) (p = <0.001). CLIF OFs score was 13.02 ± 1.97 and CLIF C ACLF was 61.67 ± 9.31 in Group 1. In Group 1, 3.3% had single organ failure, 41.7% had two organs failure and 55% have three or more organs failure. Serum level of CK 18 (M30) was significantly higher in Group 1 [13.1 ng /ml (2–31.8 ng /ml)] compared to Group 2 [5.7 ng /ml (3.0–13.6 ng/ml)] and Group 3 [3.0 ng/ml (1.6–4.1 ng/ml)] (p = 0.017, p = <0.001). The area under the receiver operating characteristic curve (AUC) for serum CK 18 (M30) in diagnosis of ACLF was 0.902 (95% CI = 0.833–0.970) at cut off level of 3.45 ng/ml. The sensitivity was 85%,the specificity was 93.3%, positive predictive value was 98.1%, negative predictive value was 60.8%and accuracy was 86.7%. There was significant positive correlation between serum level of CK 18 (M30) and CLIF C ACLF score (r = 0.331,p = .01). Logistic regression analysis showed that serum CK 18 (M30) level was independently associated with ACLF (OR = 2.72, 95% CI = 1.14–6.5). There was no significant difference in serum CK 18 (M30) level between infection precipitated ACLF and all other causes of ACLF (p = 0.476).
Conclusion: Serum cytokeratin 18 (M30), a marker of caspase-mediated apoptosis, at cut off value of 3.45 ng/ml can diagnose acute on top of chronic liver failure in chronic HCV cirrhosis with high accuracy regardless of the precipitating insult. Its serum level is positively correlated with ACLF severity as evaluated by CLIF C ACLF score.

THU173

Air-liquid interactive bioartificial liver embedded with 3D-layered human hepatocyte-derived liver progenitor-like cells rescues pocine acute liver failure

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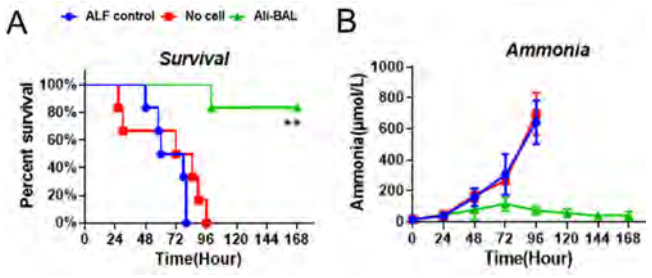
Background and Aims: Clinical advancement of bioartificial liver is hampered by the lack of expandable functional human hepatocytes and appropriate bioreactor/carriers supporting their three-dimensional (3-D) constructs. Here we developed a novel air-liquid interactive 3-D bioartificial liver (Ali-BAL) with the use of immortalized human hepatocyte-derived liver progenitor-like cells (iHepLPCs) and evaluated the safety and effectiveness of the device in a porcine model of drug-overdose acute liver failure (ALF).
Method: HepLPCs were immortalized and then functionally enhanced by selective screening of hepatic transcription factors. The cells were expanded in microfiber network on a large scale in Ali-BAL in which cells grew into 3-D structures on macroporous carriers and were alternately exposed to aeration and nutrition. Animals received infusion of hepatotoxin D-galactosamine and then were treated with Ali-BAL. Blood ammonia, liver function and coagulation index were measured every 24 h. Cytokine arrays were used to determine the proinflammatory cytokines. Hematoxylin and eosin

(H&E) staining and immunohistochemistry were used to examine liver injury and regeneration.
Results: iHepLPCs exhibited efficient expansion without growth arrest. Overexpression of FOXA3 significantly improved the synthesis, secretion and detoxification functions of iHepLPCs. When cultured on macroporous carriers in Ali-BAL, not only sufficient cell yield was obtained, but the cells formed 3-D constructs, leading to further enhanced liver functions. After Ali-BAL treatment, ALF porcine had markedly improved survival (83%, n = 6) compared to ALF control (17%, n = 6, p = 0.02) and No-cell device therapy (0%, n = 6, p = 0.003). The blood ammonia levels, as well as biochemical and coagulation indices were significantly reduced in Ali-BAL-treated pigs. Ali-BAL treatment attenuated liver damage, ameliorated inflammation and enhanced liver regeneration.



Conclusion: Novel air-liquid interactive bioartificial liver embedded with 3D-layered iHepLPCs can improve ALF porcine survival. The Ali-BAL might be considered as a new therapeutic device for ALF treatment.

THU174

Outcomes following deceased and live donor liver transplantation for the indication of acute liver failure: a multicenter experience

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Background and Aims: The aim of the present study was to evaluate the characteristics of patients with acute liver failure (ALF) who underwent liver transplantation (LT) at 14 centers in Turkey and to determine factors associated with mortality.
Method: Between 2002 and 2019, adult and pediatric patients who have received LT with the diagnosis of ALF were enrolled into the study. Data was transferred into the electronic case report form on the web site of Acute Liver Failure and Liver Transplantation Special Interest Group (SIG) of Turkish Association for the Study of the Liver (TASL). The recipients were followed in the outpatient setting with regular intervals. Physical examination was performed and laboratory tests were obtained.
Results: Among 6944 recipients with LT, 335 patients (5%) were transplanted for ALF: 238 (144 female and 94 male) were adult, and the remaining 97 (45 female and 52 male) were pediatric cases. Mean age of adults was 36.8 ± 13.6 years, whereas it was 7.7 ± 5.4 years for pediatrics. Most common etiologies among adults were: i) viral hepatitis (32.0%, of which, 88.0% were due to acute HBV), ii) indeterminate (27.3%), and iii) drugs/toxins (26.1%, of which 29.0% were mushroom poisoning). Among children, etiologies were: i) indeterminate (37.1%) and ii) drugs/toxins (30.0%). Living-donor liver transplantation (LDLT) was performed among 221 patients (66%), whereas deceased donor liver transplantation (DDLT) was performed in 114 patients (34%). Overall survival was 70% (235/335) with a median (range) follow-up of 110 (0–884) weeks. Survival was better among the patients who underwent LDLT than those of patients who underwent DDLT (mean 675.2 ± 26.3 vs 395.5 ± 36.7 weeks, respectively, p < 0.001). Survival was slightly better in the adult group compared to the pediatric group (568.2 ± 24.1 vs 550.7 ± 50.0 weeks, respectively, p = 0.15). A multiple cox regression analysis showed that patient age at diagnosis, number of days waiting for LT, donor type (DDLT vs LDLT), pre-transplant high sodium level, high MELD and the presence of hepatic encephalopathy (grade II-IV) were associated with mortality.
Conclusion: Based on the early results of the present multicenter study, hepatitis B virus infection is still major cause of liver-related morbidity and mortality in Turkey. Long-term post-transplant survival is favorable in patients with ALF. LDLT may have improved the overall survival among recipients for ALF.

THU175

Expression of microRNA-124 in Kupffer cells modulates liver injury

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Background and Aims: MicroRNA-124 (miR-124) is related to liver injury subjected to chronic hepatitis B (CHB) and hepatitis B virus related acute-on-chronic liver failure (HBV-ACLF). However, the mechanisms of miR-124 regulating liver inflammation are largely unknown. In this study, we tested the hypothesis that miR-124 highly expresses in Kupffer cells and modulates liver inflammation through effects on the interleukin (IL)-6 pathway.
Method: The role of miR-124 in acute liver injury was assessed in Concanavalin A (ConA) induced mice model. Four hepatic nonparenchymal cells were isolated from liver tissues of mice. Expression of IL-6, signal transducer activator of transcription 3 (STAT3), and phosphorylated-STAT3 (p-STAT3) was investigated in Kupffer cells of mice. miR-124 expression was determined in CHB and HBV-ACLF patients, with miRNA array and quantitative real-time PCR. Biological functions of miR-124 were studied using immunohistochemical.

Luciferase reporter assays and Western blots were performed to identify miR-124 targets.
Results: miR-124 expression was significantly elevated in CHB and HBV-ACLF patients and mice with acute liver injury. Besides, miR-124 was highly expressed in Kupffer cells both in human and mice. While IL-6 expression was dramatically decreased by miR-124 overexpressed plasmid injection in mice. Moreover, mRNA levels of STAT3 and protein levels of pSTAT3 were inversely correlated with those of miR-124. miR-124 inhibited IL-6-mediated proinflammatory effects in vitro and liver inflammation in vivo, through a mechanism involving direct targeting of the 3'-untranslated region of STAT3.
Conclusion: Our findings suggest that upregulation of miR-124 relieve liver inflammation through the IL-6/STAT3 pathway.

THU176
Predictors of acute liver failure and death among patients with dengue-induced severe hepatitis

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Background and Aims: Liver injury is common however severe hepatitis is rare in dengue viral infection. We aimed to identify prognostic predictors of acute liver failure (ALF) and death of patients with dengue-induced severe hepatitis (DISH).
Method: We retrospectively reviewed 2,311 serology-confirmed adolescent and adult dengue patients who were hospitalized during the 12-year study period (between 2007 and 2019). Patients with DISH [n = 134 (5.80%)], defined as baseline transaminase ≥ 10 times, and DISH with subsequent ALF, defined by the EASL 2017 criteria, [n = 17 (0.74%)] were included. Predictors of ALF and in-hospital death were identified using logistic regression analysis.

Table: Multivariate analysis of factors associated with acute liver failure and death from dengue-induced severe hepatitis

	Acute liver failure			Death		
Factors	Adjusted Odd ratio	95% confidence interval	p-value	Adjusted Odd ratio	95% confidence interval	p-value
INR	2.40	0.37–15.46	0.36	7.03	1.20–41.12	0.031
Albumin	0.48	0.11–2.13	0.34	0.35	0.07–1.81	0.21
Creatinine	0.81	0.42–1.57	0.53	1.20	0.63–2.27	0.58
MELD score	1.23	1.01–1.49	0.039	0.96	0.79–1.17	0.70
Presence of liver co-morbidities	0.59	0.06–5.45	0.64	0.21	0.01–4.51	0.32

Results: Of the 151 patients, 53% were female, with a median age of 23 years. Capillary leakage syndrome (CLS) occurred in 64.2% of DISH and 100% of ALF patients. The mortality rate was low in DISH (0.7%), but was remarkably high if ALF developed (58.5%). By univariate analysis, age, sex, hematocrit, white blood count, atypical lymphocyte count, platelet count, INR, SGOT, SGPT, ALP, albumin, creatinine, MELD score, alcohol consumption, presence of liver co-morbidity and presence of CLS, were identified as potential prognostic parameters for ALF or death. By multivariate analysis (Table), MELD score was the only factor that remained associated with ALF with adjusted odd ratio (AOR) of 1.23 (95% confidence interval (CI) 1.01–1.49), p = 0.039. Regarding mortality prediction, the deterioration of liver function to ALF was the most significant factor related to death in DISH patients (AOR 394.00, 95%CI 4.01–38845.94, p = 0.011). Other independent factors associated with death included baseline INR (AOR 7.03, 95%CI 1.20–41.12, p = 0.031). INR ≥ 1.5 predicted death from DISH with AUROC of 0.832, 81.8% sensitivity and 86.8% specificity.
Conclusion: High MELD score was the best predictor of ALF in dengue viral infection. The presence of ALF was the major risk of death from DISH.

THU177
Clinical and radiological features for early identification of malignancy induced acute liver failure

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Background and Aims: Acute Liver failure (ALF) caused by malignant infiltration (ALF-M) as the first presentation of a neoplastic disease is an extremely rare cause of ALF. It is crucial to reach a correct diagnosis for consideration of appropriate treatment and to avoid liver transplantation (LT). We sought to identify features enabling earlier diagnosis of ALF-M in patients with ALF without a clear initial cause.
Method: Analysis of clinical, laboratory and radiologic features of patients presenting to King's College Hospital with ALF-M between 1999–2019 compared to patients with LF of indeterminate cause (ALF-I). All patients had liver imaging with a CT scan, US or both. For patients with available CT scans, observed and predicted liver volume (LV) was determined.
Results: Of the 35 ALF-M patients, 51% were male with median age 54 years (range 19–73). Among 50 patients presenting with ALF-I, 32% were male with median age was 46 years (range 20–70, p = 0.04). Hematological malignancies were diagnosed in 63% of ALF-M, most commonly lymphoma (68%). Among those with solid malignancy, 58% were poorly differentiated adenocarcinoma. ALF-M diagnosis was made post-mortem in 31%, one patient with ALF-M underwent LT and was diagnosed on explant. In both groups the most common presentations were jaundice (65%) and abdominal pain (35%). Nausea, vomiting and pruritus were more common among patients with ALF-I; fever, weight loss and night sweats were more frequent with ALF-M. Mortality in ALF-M patients was 91% vs. 22% in ALF-I (p < 0.001), with median interval from admission to death 7 days (range 1–70). In patients with ALF-M median predicted LV was 1591 cm^3 and 88% of the patients had a larger then expected LV. Observed LV was 2331 cm^3 (range 1132–6347 cm^3), 149% of expected (range 71–411%); in comparison to the ALF-I group where liver volume was reduced with median LV of 1112 cm^3 (range 445–2910 cm^3, p = 0.001), 70% of predicted LV (range 28–260%, p < 0.001). ALF-M patients also had higher Alkaline-phosphatase, CRP (P < 0.001), ferritin (P < 0.05) and Lactate Dehydrogenase (P < 0.01) levels. On multivariate logistic regression, LV remained an independent predictor of ALF-M over ALF-I (P < 0.001).
Conclusion: ALF-M may be differentiated from indeterminate disease by clinical features of age, gender and systemic symptoms. It has characteristic laboratory findings and is strongly associated with hepatic enlargement.

THU178
Deletion of XBP1 in liver parenchymal cells ameliorates acetaminophen (APAP)-induced hepatotoxicity via activation of IRE1alpha-JNK1-ATG5-dependent autophagy

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Background and Aims: Drug-induced liver injury (DILI) is a leading cause of acute liver injury, including acetaminophen (APAP) overdose. APAP-mediated hepatotoxicity induces the unfolded protein response (UPR), a signalling cascade that triggers endoplasmic reticulum (ER) stress and splicing of the X-binding protein 1 (Xbp1). However, the mechanisms underlying ER stress remains poorly understood, thus dampening the chances of pharmacologic therapy for DILI patients.
Method: Mice harboring a conditional floxed allele of Xbp1 ($Xbp1^{f/f}$) were crossed with Alb-Cre expressing strain to obtain a liver specific knockout of Xbp1 ($Xbp1^{\Delta hepa}$). For these experiments, fasting male mice aged 10–12 weeks, were challenged with APAP (500 mg/kg, i.p.). APAP was first dissolved in DMSO and then diluted into 50 mg/ml (final concentration of DMSO was 0.09%). Control mice received an equivalent volume of PBS with DMSO. Mice were sacrificed 0–48 h later and tissues collected. Histopathological examination of livers, immunofluorescence (IF) and immunohistochemistry (IHC), Western blot, Real Time (RT)-qPCR studies and transmission electron microscopy (TEM) were performed.
Results: Mice with deletion of Xbp1 in liver parenchymal cells (LPC) showed significantly less mortality to APAP than floxed littermates. Twenty-four hours later, $Xbp1^{\Delta hepa}$ animals displayed a significant dramatic decrease in serum ALT, AST and LDH levels in response to 500 mg/kg of APAP, compared with $Xbp1^{f/f}$ mice. Concomitantly, reduced necrotic foci in the liver parenchyma, TUNEL-detected hepatocyte death and maintenance of hepatocyte polarity – evaluated with ZO-1 IF - was characteristic of $Xbp1^{\Delta hepa}$ animals. Less hepatic lipid accumulation evidenced by Oil Red O (ORO) staining alongside triglyceride and cholesterol levels were dramatically reduced in livers of $Xbp1^{\Delta hepa}$ mice. Transcription of CYP2E1 was drastically diminished in $Xbp1^{\Delta hepa}$ mice, associated with significantly lower oxidative stress (e.g.: 4-HNE and DHE). Next, we investigated the UPR in these conditions. Increased mRNA and protein expression of pIREα, associated with decreased BIP, CHOP were observed in $Xbp1^{\Delta hepa}$ group. TEM analysis showed abundance of lipid bodies and autophagosomes in $Xbp1^{\Delta hepa}$ animals. Interestingly, ablation of Xbp1 in LPC triggered JNK1 and ATG5 overexpression, and downregulation of p62.
Conclusion: Our study overall demonstrated that Xbp1 deficiency in LPC ameliorates APAP-derived DILI via activation of autophagy in an IRE1α-JNK1-ATG5-dependent mechanism. This novel finding provides the basis for therapies targeting the restoration of LPC function after acute liver injury.

THU179

Larazotide acetate reduces the frequency of bacterial translocation in the thioacetamide-induced liver failure in rats

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Background and Aims: Increased mucosal permeability is one of the possible mechanisms that could increase bacterial translocation (BT) in liver failure. Intestinal epithelial barrier function relies on tight junction proteins, such as occludin and Z0–1, which may be regulated in part by endogenous zonulin release. Larazotide acetate (LA) (Innovate Biopharmaceuticals, Inc., Raleigh, NC, USA) is a synthetic octapeptide that reduces tight junction permeability by blocking zonulin receptors, although other mechanisms are being explored. Presently, LA is being studied in Phase 3 clinical trials for treatment of Celiac disease. In this study, we aimed to investigate the effect of LA on BT in a thioacetamide-induced liver failure model in rats.
Method: A total of 48 rats were divided 6 groups (n = 8 rats/group) as follows: Group I (Control), 0.1 ml i.p. 0.9% NaCl for 7 days; Group II (TAA), 300 mg/kg/day i.p. thioacetamide (TAA) every 24 h for 3 days; Group III (TAA + LA), 300 mg/kg/day i.p. TAA 3 days + 0.01 mg /ml LA in the drinking water for 7 days, initiated before the first dose of TAA; Group IV (LA): LA in the drinking water for 7 days with no TAA treatment; Group V (TAA + gavaged LA): 300 mg/kg/day i.p. TAA for 3 days + gavaged LA (300 μl of 0.1 mg/ml) twice a day for 7 days initiated before the first dose of TAA; Group VI (gavaged LA): Gavaged LA twice a day for 7 days (300 μl of 0.1 mg/ml). BT was defined as positive bacterial cultures from mesenteric lymph nodes, liver, or spleen samples. Liver and intestine samples were taken for histopathological examination.
Results: Significant intestinal and liver damage was observed in the TAA group when compared with control, LA-drinking water, and LA-gavaged groups. Serum AST, ALT and ammonia levels in the TAA group were significantly higher than those in the other groups. The frequency of BT in the TAA+LA-drinking water group was significantly lower than in the TAA group (28.5% and 62.5%, respectively, $p < 0.05$). Intestinal damage scores in the TAA+LA-drinking water was lower than in the TAA group ($p < 0.05$). In the TAA + LA-drinking water and TAA + LA-gavage groups, close apposition between the villus epithelial cells in the region of the tight junctions was observed.
Conclusion: Our results suggest that Larazotide reduces the frequency of bacterial translocation by reducing intestinal barrier breakdown as compared to the TAA-induced liver failure rats in the absence of LA. These studies reveal a potential therapeutic benefit of LA for important liver diseases such as NASH and NAFLD.

THU180

The protective effects of a sense oligonucleotide drug targeting inducible nitric oxide synthase for a rat model of acute liver injury

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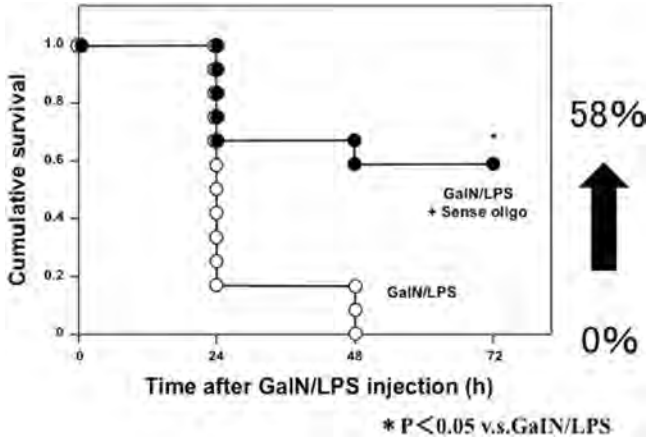
Background and Aims: From rat, mouse, and human genes that encode inducible nitric oxide synthase (iNOS), natural antisense transcripts (asRNAs) that do not encode proteins are transcribed. iNOS catalyzes the production of the inflammatory mediator nitric oxide (NO), which is excessively produced in hepatocytes and macrophages in septic shock. The iNOS asRNA stabilizes iNOS mRNA by interacting with the iNOS mRNA. We found that single-stranded sense oligonucleotides corresponding to the sequence of iNOS mRNA decreased iNOS mRNA levels by interfering with the mRNA-asRNA interactions in hepatocytes. The iNOS sense oligonucleotides that were substituted with locked nucleic acids and phosphorothioate bonds and efficiently reduced the levels of iNOS

mRNA and iNOS protein. Here, we investigated in vivo effects of the iNOS sense oligonucleotides in acute liver injury model rats.
Method: Each iNOS sense oligonucleotide (SO1 or its derivatives) was introduced into primary cultured rat hepatocytes, and the expression levels of iNOS mRNA were measured in the presence of interleukin 1beta and compared to the cells transfected with control DNA. A sepsis model was prepared by the administration of D-galactosamine (GalN) and bacterial lipopolysaccharide (LPS) with or without the injection of an iNOS sense oligonucleotide to rats. Survival of the treated rats was recorded by 72 h after GalN/LPS injection, and the expression of iNOS and cytokine mRNAs in the liver were analyzed. Liver tissues of the treated rats were pathologically examined.
Results: Among prepared iNOS sense oligonucleotides, which include chemically modified derivatives, SO1 was the most effective oligonucleotide for decreasing expression level of iNOS mRNA in rat hepatocytes. When SO1 was simultaneously administered with GalN and LPS to rats (GalN/LPS+SO1 group), their survival rate was markedly increased (58%) compared to the rats administered with GalN and LPS alone (GalN/LPS group)(Fig). The expression of the iNOS and TNF-alpha mRNAs was decreased, and the number of apoptotic hepatocytes were also significantly suppressed in the livers of GalN/LPS+SO1 group compared to that of GalN/LPS group.



Conclusion: Administration of an iNOS sense oligonucleotide inhibited the induction of iNOS and TNF-α in sepsis model rats and showed hepatoprotective effects by the improvement of the pathological findings in the liver. These data imply that natural antisense transcript-targeted regulation (NATRE) technology using the iNOS sense oligonucleotide may be applied to treat human sepsis with acute hepatic failure.

THU181
Hasi-iquest: investigating viral etiologies of acute liver failure of unknown cause

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Background and Aims: In France, 18% of acute liver failure (ALF) are of unknown cause (ALFUC). Some ALFUC could be due to non-tested viruses. Furthermore, other ubiquitous viruses, such as EBV and TTV, whose viral loads change with immunosuppression state, could impact patients' prognosis. The main objective of our study was to describe the virological screening performed at admission for ALF in France. We also aimed to search for viral causes which had not been previously found, to describe patients' characteristics, to determine prognostic factors and to evaluate the prognostic role of ubiquitous viruses.

Method: HASIPRO is a national prospective cohort studying ALFUC. Between 2013 and 2016, 70 patients with ALFUC from 15 centers were included. Inclusion criteria were: age ≥ 18 years, severe ALF defined by INR>1.5, absence of identified cause at admission or chronic liver disease. Viral tests were performed via real-time PCR and serologies on a biobank. A blind histological review was completed to evaluate the probability of a viral cause, according to the presence of histological lesions compatible with a viral hepatitis.
Results: Hepatotropic viruses (HAV, HBV, HCV, HEV) were investigated in more than 90% of cases, versus only 19% to 69% for non-hepatotropic viruses (Table 1). Viral screening methods were heterogenous and did not follow EASL guidelines: HSV-1 and HSV-2 were investigated both via PCR and serology in only 25% of patients. Six ALFUC cases (8.5%) were reconsidered viral (HEV, n = 3; dengue, n = 1; Parvovirus B19, n = 2). Among them, one died (17%) and another one underwent liver transplantation (17%). Their characteristics were not different from those with non-viral ALFUC.

Table 1: Percentage of methods used to detect viruses in 70 patients with ALFUC

	PCR	IgM	IgG	Other method
HBV	36	94		100
HAV	3	**99**		
HCV	44	**99**		
HEV	46	**90**		
CMV	**69**	73	91	
HSV-1	**57**	54	63	
HSV-2	**56**	49	57	
EBV	**49**	79	89	
HHV-6	**40**	14	14	
VZV	**26**	36	46	
Parvovirus B19	**19**	33	34	
Rubella	**1**	6	11	

In bold: baseline diagnostic method.

The probability of a viral cause based on histological review was considered "Possible" in 14 cases (56%) on liver biopsies and 15 cases (75%) on explanted liver samples. Necrosis percentage ($p = 1.0$) and fibrosis score ($p = 0.77$) were not prognostic factors of mortality or liver transplantation.
Ubiquitous viruses EBV and TTV were detected in 49% and 78% of cases respectively but were not prognostic factors of mortality or liver transplantation ($p = 0.06$ and $p = 0.97$).
Conclusion: This is the first study to prospectively search for a viral cause in patients with ALFUC. Even though cases of ALFUC later reclassified as viral are rare (8.5% of patients), the viral investigations conducted in French centers are heterogenous and do not fully respect international guidelines. Liver biopsies do not provide supplementary information when a viral cause is suspected. Ubiquitous viruses do not seem to play a prognostic role in patients with ALFUC.

THU182
Poly(adp-ribose) polymerase plays a critical role in oxidative stress- and hypoxia/reoxygenation-induced programmed cell death in mouse liver cells

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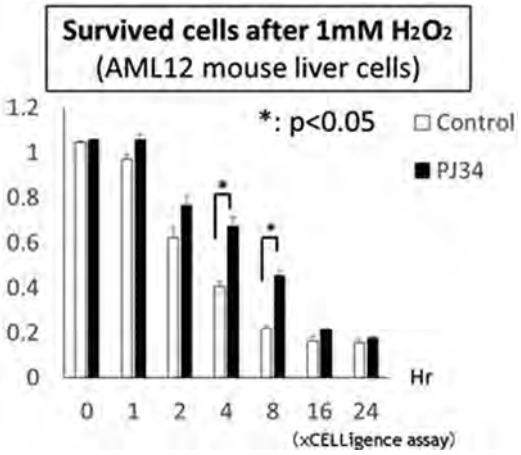
Background and Aims: Ischemia/reperfusion (I/R) of liver is an unavoidable event in liver surgery and transplantation, which sometimes causes serious post-operative liver failure, leading to life-threatening complications. The mechanism of I/R-induced liver injury, however, seems to be complicated so that we have not elucidated yet. Recently, various types of programmed cell death have been newly reported, including ferroptosis, necroptosis, pyroptosis,

and parthanatos. In the present study, we investigated the roles of PARP [Poly(ADP-ribose) polymerase] on oxidative stress- and hypoxia/reoxygenation (H/R)-induced programmed cell death in AML12 mouse liver cells.

Method: The mouse liver cells (AML12) were used for the experiments. AML12 cells were cultured in high-glucose DMEM supplemented with 10% FBS. H2O2 were administered directly to the culture medium for oxidative stress. Cellular hypoxic conditions were created and maintained in a chamber by flushing with a 95% N2/5% CO2 gas mixture for 10 min and then sealing the chamber. Following 6 h of hypoxia, AML12 cells were reoxygenated by opening the chamber and replacing the hypoxic medium with oxygenated medium. Protein and gene expressions were measured by western blot analysis/capillary-based immunoassay and RT-PCR, respectively. Cell survival and death were determined by plating the cells in the xCELLigence System (Roche) and the LDH release from hepatocytes into culture medium.

Results: H/R-induced cell death was inhibited significantly by PJ34, a specific inhibitor of PARP. Because an oxidative stress is one of the major causes of H/R-induced cell death, we challenged 1 mM H2O2 to AML12 liver cells. H2O2 induced cell death, PAR [Poly(ADP-ribose)] production and nuclear translocation of AIF (apoptosis inducing factor), which were suppressed significantly by the pre-treatment of PJ34 (Figure). H2O2 also induced Receptor-Interacting Protein (RIP)1/RIP3 binding, which indicates the involvement of necroptosis in H2O2-induced cell death. Interestingly, H2O2-induced RIP1/RIP3 binding was also inhibited by PJ34. These facts indicate that H/R and oxidative stress potentially induce parthanatos and necroptosis in hepatocytes.



Conclusion: PARP is potentially involved in H/R- and oxidative stress-induced cell death in mouse liver cells, by inducing parthanatos and necroptosis.

THU183

Investigation into the cut-off point for chronicity of drug-induced liver injury through metabolomic profiling

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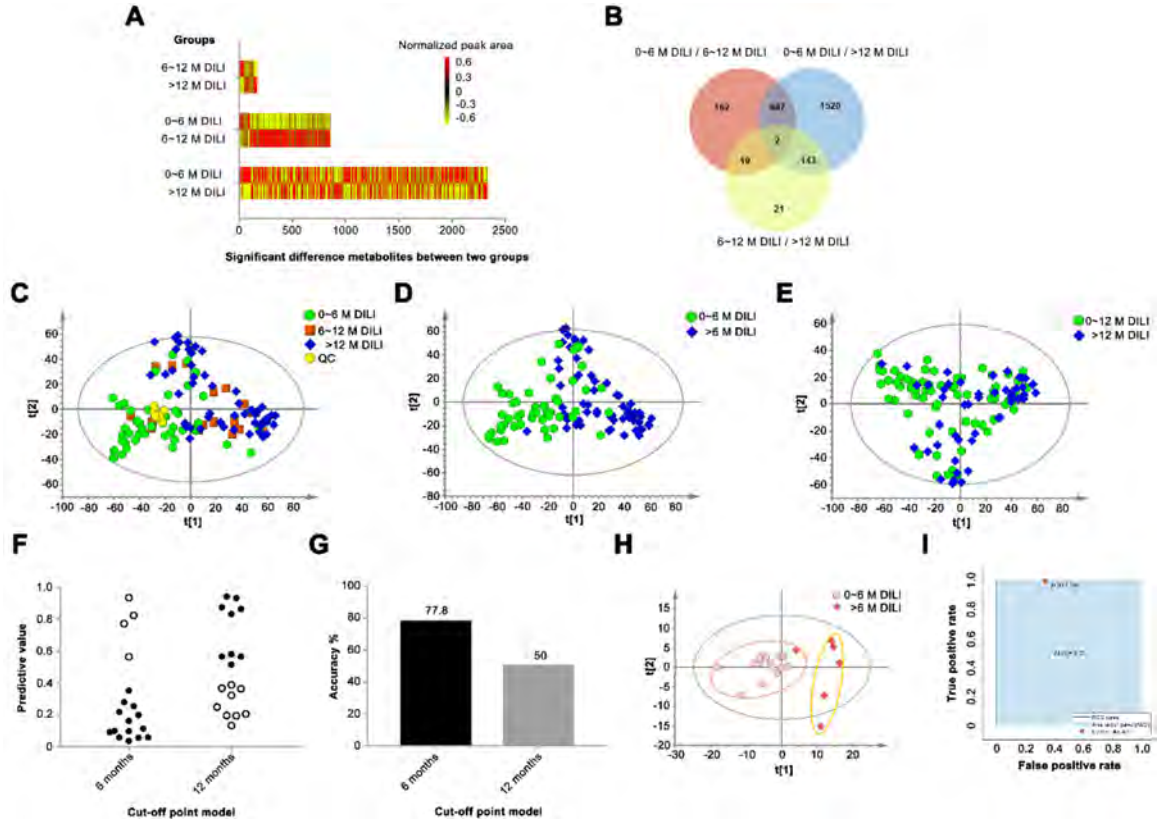

Figure: (abstract: THU183): (A) Serum metabolites with significant differences between each two groups. The color indicates the normalized peak area of the metabolites between each two groups. The X axis indicates the number of metabolites with significance. (B) The Venn diagram of metabolites with significant differences within each two groups. (C) PCA plot of 0~6 M DILI, 6~12 M DILI and >12 M DILI groups. (D) PCA plots of 0~6 M DILI and >6 M DILI groups. (E) PCA plot of 0~12 M DILI and >12 M DILI groups. (F) Predictive accuracy by LDA modelling at different cut-off points. Box plot of the LDA models at cut-off point of either 6 or 12 months to predict DILI patients with 6~12 months duration. Blank circles indicate the false predicted samples and solid circles indicate the true prediction. (G) Predictive accuracy (%) of the LDA models established by different cut-off points. (H) External validation in the prospective cohort of Center 2. PCA plot of 0~6 M DILI and >6 M DILI groups. (I) ROC diagram of LDA model in separating 0~6 M DILI and >6 M DILI groups.

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Background and Aims: Chronicity is an unsolved problem and a challenge in the field of drug-induced liver injury (DILI). Since there are discrepancies in the cut-off point for the definition of chronicity in DILI, it inevitably leads to incomparability among different studies.
Method: In this study, we divided the involved DILI cases into Group 1 (0~6 months), Group 2 (6~12 months) and Group 3 (>12 months) based on the duration of liver injury, and then performed high-resolution mass spectrometry-based serum metabolomic profiling. All of the differential metabolites with statistical significance within every two groups were selected as the potential biomarkers of duration-related characteristics.
Results: By using these 2,554 characteristic metabolites, the unsupervised principal component analysis represented a two-cluster pattern of the aforementioned three groups with 6 months as a rough separatrix. The following linear discrimination analysis showed that the cut-off point at 6 months was better than that at 12 months. The cut-off of 6 months was then validated independently in the prospective cohort at an external center.

Conclusion: Taken together, our results provided the first experimental evidence to support the duration of 6 months as the rational cut-off point in defining chronicity in DILI.

THU184

Hepatic steatosis predicts fibrosis in long-term methotrexate use

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Background and Aims: Methotrexate (MTX) is effective for dermatologic and rheumatologic conditions such as psoriasis (Ps), psoriatic arthritis (PsO) and rheumatoid arthritis (RA). Long-term MTX use may be complicated by hepatic fibrosis, although patient, disease factors and the mechanism remain unclear. Transient elastography (TE) is a non-invasive measure of hepatic fibrosis that is often used as surveillance in this patient population.
Patients with Ps and PsO have higher rates of non-alcoholic fatty liver disease. The controlled attenuation parameter (CAP) measurement is a non-invasive test that correlates with histologic degree of steatosis. To our knowledge, no studies have evaluated hepatic steatosis via CAP scores in MTX use.
The aim was to determine the prevalence of hepatic steatosis and predictors of hepatic steatosis and fibrosis in persons on MTX.
Method: A single centred retrospective cohort study was performed. Patients on >6 months of MTX for a dermatologic or rheumatologic disease who had undergone TE from January 2015 to September 2019 were included. Demographic variables, laboratory investigations, TE and CAP scores were collected. Multivariate analysis was performed to determine predictors of steatosis and fibrosis.
Results: A total of 177 patients on methotrexate were included. Ps was the most frequent diagnosis (n = 52) followed by RA (n = 50) and PsO (n = 38). Steatosis (CAP>245 dB/m) was present in 73.9% of patients. Patients with steatosis had significantly more fibrosis and a higher BMI than those without steatosis (CAP < 245 dB/m). Higher CAP score was correlated with increased lifetime dose of methotrexate by Pearson correlation analysis (r = 0.48, p = 0.001) (n = 85 patients). Multivariate regression analysis revealed that diabetes mellitus (OR 10.5, 95% CI 1.38–80.60), hypertension (OR 4.97, 95% CI 1.66–14.84), and BMI>30 (OR 10.1, 95% CI 1.88–37.14) were predictors of steatosis (CAP>245 dB/m). Predictors of METAVIR>F2 (TE>8.0 kPa) by multivariate regression analysis included CAP score of >270 (OR 8.36, 95% CI 1.88–37.14), diabetes mellitus (OR 2.85, 95% CI 1.09–7.48), hypertension (OR 5.4, 95% CI 2.23–13.0), dyslipidemia (OR 3.71, 95% CI 1.50–9.18) and alcohol use (OR 3.06, 95% CI 1.2–7.49).
Conclusion: In patients on MTX for rheumatologic and dermatologic diseases, hepatic steatosis was prevalent and predicted higher grades of fibrosis. Additionally, increasing MTX exposure is correlated with steatosis. Features of the metabolic syndrome including diabetes, hypertension and obesity were predictors of both steatosis and fibrosis. Further study is needed to evaluate if steatosis is a mechanism by which fibrosis occurs in patients on MTX, or if it due to other patient factors.

THU185

Novel therapy with anti-miR-873-5p at late stages of acetaminophen overdose

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Background and Aims: The liver has a major role in maintaining homeostasis and is in charge of xenobiotic metabolism. Acetaminophen (paracetamol or APAP) is commonly used to treat pain and fever worldwide. Its overdose is the most common cause of Drug-Induced Liver Injury (DILI) and Acute Liver Failure (ALI) in the United States and in the majority of Europe, being Acetylcysteine (NAC) the standard treatment for acetaminophen overdose. However, its use is limited, as NAC is effective at 8 h after ingestion, so alternative approaches are needed. It is known that Glycine N-methyltransferase (GNMT) expression is reduced in different liver diseases. It is known that GNMT, the main enzyme implicated in S-adenosylmethionine catabolism in the liver, is reduced in different liver diseases. Further, we have recently identified that miR-873-5p mediated repression of GNMT compromises hepatocyte and mitochondrial functionality. The aim of this work is to study the implication and potential therapeutic targeting of miR-873-5p/GNMT axis in APAP-induced liver injury.
Method: Analysis of miR-873-5p was performed in human serums from patients with different DILI scores (n = 40). Primary hepatocytes were transfected with anti-miR-873-5p or anti-miR-Control and the response was evaluated 1, 3 and 6 hours after APAP administration (10%). Besides, C57BL/6J mice were exposed to 300 mg/kg APAP and treated with anti-miR-873-5p (60 µg/mice) or anti-miR-Control (60 µg/mice) at 6 (n = 5) and 24 hours (n = 5) after APAP overdose. Mice were sacrificed after 48 h of APAP administration.
Results: The protective role of anti-miR-873-5p in DILI has been characterised, both *in vivo* and *in vitro*, via methionine and polyamine cycles refeeding. Higher levels of miR-873-5p were detected in serum samples from DILI patients. Anti-miR-873-5p treated mice showed significantly reduced levels of liver transaminases and ROS, increased GSH/GSSG and decreased concentration of TNF in serum in the 24h-group. The metabolomic analysis of liver tissue revealed higher levels of spermidine in anti-miR-873-5p treated mice (24 h-group).

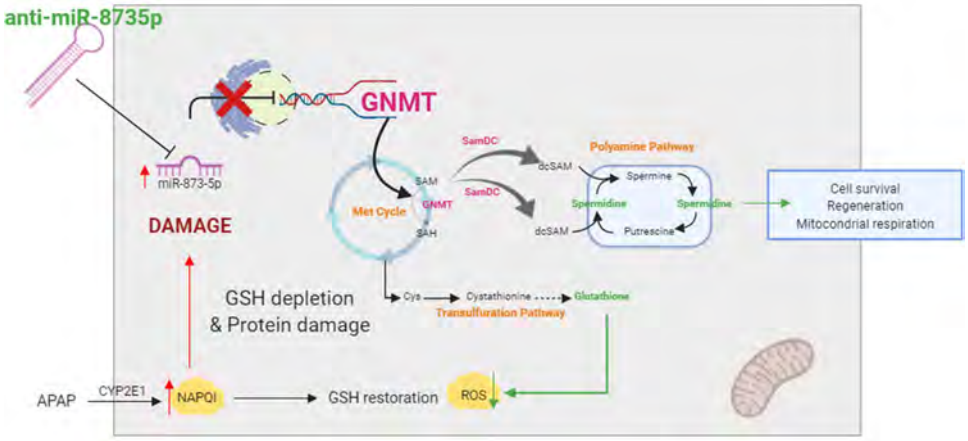

Figure: (abstract: THU185)

Spermidine levels correlate with enhanced mitochondrial functionality, respiration and regeneration via GSK3β/β-catenin/cyclin-D1 pathway. ATP and mitochondrial respiration were also significantly higher in hepatocytes with anti-miR-873-5p (at 1 h).
Conclusion: During APAP-induced liver injury, GNMT expression is downregulated by miR-873-5p. The present study showed that 1- miR-873-5p could be a potential biomarker in DILI and 2- anti-miR-873-5p could be a suitable therapeutic agent as protects the mitochondria, reduces inflammation and induces liver regeneration by restoring GNMT levels. Overall, anti-miR-873-5p treatment prevents APAP-induced liver injury, even long time after the overdose, then, 3- this therapy could be an alternative at times in which NAC is not efficient.

THU186

A novel HER2-targeted liposomal formulation for reducing the risk of liposome-induced hepatotoxicity

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Background and Aims: Stealth immunoliposomes (SILs) are nanosystems obtained by conjugating monoclonal antibodies or antibody fragments to fractions of poly-ethylene-glycol (PEG)-phospholipids present in stealth liposomes. It has been shown that these nanosized materials can accumulate into the liver, causing drug-induced liver injury. The aim is to improve the pharmacokinetic and toxicological profile of encapsulated drugs and permit targeted therapy.
Method: We evaluated the pharmacokinetics and hepatotoxicity of two HER2-targeted SILs obtained by conjugating trastuzumab Fab' with classic PEG-phospholipids (SIL) or with a novel mPEG-branching-(phospholipid)$_2$ ($SSIL_2$). Both formulations were loaded with doxorubicin. 2.5 mg/kg of doxorubicin equiv. SIL or $SSIL_2$ was administered via caudal vein to Sprague-Dawley rats (n = 6 per group). Vehicle-administered rats were used as controls. Rats were sacrificed 48 hours after treatment. Hepatotoxicity was assessed by 1) standard histological analysis (H&E) performed on liver sections; 2) full blood count and plasma liver function tests; 3) hepatic mRNA level for IL-1β, TNF-α, IL-10, CCL2 and CXCL2; 3) reactive oxygen species (ROS) production in liver tissue. Data were compared by one-way ANOVA followed by Tukey *post-hoc* test.
Results: $SSIL_2$ showed an improved pharmacokinetic profile compared to SIL, since elimination half-life increased ($p < 0.05$), while systemic clearance of doxorubicin tended to drop. SIL caused hepatotoxicity, as indicated by the decrease of plasma albumin ($p < 0.05$ *vs* controls), the presence of several hepatic granulomatous lesions, granulocytes, and macrophages, and confirmed by increased hepatic CXCL2 and IL-10 mRNA levels ($p < 0.001$ *vs* controls). Accordingly, IL-1β and TNF-α mRNA expression and ROS concentration increased significantly ($p < 0.001$) in these rats. At variance, histological analysis revealed only few isolated granulomas in $SSIL_2$-treated animals, and the other parameters were similar to those of controls. Immunohistochemical staining for α-SMA excluded the presence of fibrosis in all rats.
Conclusion: The conjugation of SILs with mPEG-branching-(phospholipid)$_2$ represents an effective strategy to improve the pharmacokinetic profile of drugs and prevent the hepatoxicity associated to PEG-derived nanosystems, thus improving the efficacy and tolerability of innovative cancer therapy.

THU187

Combination of sivelestat and n-acetylcysteine alleviates the inflammatory response and exceeds standard treatment for acetaminophen-induced liver injury

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Background and Aims: Hepatocyte death during acetaminophen (APAP) intoxication elicits a reactive inflammatory response, with hepatic recruitment of neutrophils and monocytes, which further aggravates liver injury. Neutrophil elastase (NE), secreted by activated neutrophils, has degradative and cytotoxic functions and sustains a pro-inflammatory state. We investigated NE as a therapeutic target in APAP-induced liver injury.
Method: C57BL/6 mice were administered a toxic dose of APAP (300 mg/kg intraperitoneally (IP)), 2 hours prior to receiving the NE inhibitor sivelestat (150 mg/kg IP), N-acetylcysteine (NAC, 200 mg/kg IP) or a combination therapy, and were euthanized after 24 and 48 hours. Serum and liver tissue were harvested for analyses. In additional *in vitro* experiments, the chemotactic properties of NE were evaluated using peripheral blood mononuclear cells (PBMCs).
Results: Upon APAP overdose, life $CD45^+CD11b^+Ly6C^{int}Ly6G^+$ neutrophils and life $CD45+Ly6G^-$ $CD11b^+Ly6C^{hi}Tim4^-$ monocytes

infiltrated the injured liver, accompanied by increased levels of NE (p = 0.0006 versus control mice, ELISA). Combination therapy of NAC and sivelestat significantly limited liver damage, as evidenced by lower serum transaminase levels and less hepatic necrosis compared to APAP-overdosed mice without treatment, and this to a greater extent than NAC monotherapy. Only the combination of NAC and sivelestat was able to reduce the expression of hepatic pro-inflammatory markers and liver monocyte infiltration in APAP overdosed mice. Indeed, additional *in vitro* experiments confirmed the chemotactic activity of NE. Importantly, sivelestat did not impair hepatic repair in APAP-intoxicated mice as transaminase levels and hepatic necrosis were decreased at 48 hours compared to 24 hours post APAP overdose in sivelestat-treated mice.

Conclusion: Combination of NE inhibition, by using sivelestat, together with NAC dampens the inflammatory response and reduces liver damage following APAP overdose. This strategy exceeds the standard of care and might represent a novel therapeutic option for APAP-induced acute liver injury.

THU188

GSDMD inhibitor necrosulfonamide protects mice from galactosamine/lipopolysaccharide-induced acute liver failure via pyrotosis pathway

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Background and Aims: Acute liver failure (ALF) is a critical disease characterized by severe liver dysfunction and high mortality. There is no specific cure for ALF so far. Pyroptosis, with Gasdermin-D (GSDMD) being the executioner, is involved in the pathophysiological process of immune dysregulation in ALF. Necrosulfonamide (NSA) is a direct inhibitor of GSDMD and has been demonstrated to alleviate sepsis and monosodium urate crystal-induced cell death. The aim of this study was to examine the potential therapeutic role of NSA in ALF.

Method: ALF model was established by lipopolysaccharide/D-galactosamine (LPS/D-GalN) challenged in C57BL/6 mice. A dose of 20 mg/kg NSA was intraperitoneally injected 0.5 h before LPS/D-GalN challenged. The survival rate was monitored every 30 min for 24 h. Liver damage was determined by hematoxylin and eosin (HE) and serum alanine aminotransferase (ALT). Possible mechanisms involved were explored by quantitative real-time PCR, western blot and enzyme-linked immunosorbent assay (ELISA).

Results: Mice in ALF group all died within 10 h. The prognosis of mice treated with NSA was greatly improved with a 24h-survival rate of 60% (p = 0.0001, Fig. A). The liver injury features in histology, including hepatic structure collapse, hepatocytes necrosis, coagulation necrosis and inflammation, were attenuated in NSA treatment group (Fig. B, C). ALT level was significant decreased in NSA treatment group compared with ALF group (232.0 vs. 468.3; p < 0.001, Fig. D). The mRNA levels of the upstream molecules of GSDMD, including caspase-1 and caspase-11, increased in ALF group while significantly decreased after NSA pretreatment (Fig. E, F). IL-1β gene expression decreased after NSA treatment compared with ALF group (Fig. G). The protein level of GSDMD, as well as NLRP3, cleaved caspase-1, cleaved caspase-11, and IL-1β was higher in ALF than control, and significantly decreased after NSA pretreatment (Fig. H). Serum IL-1β level examined by ELISA was significant decreased in NSA treatment group compared with ALF group (55.63 vs. 110.9; p < 0.01, Fig. I).

Conclusion: Pyroptosis is activated in LPS/D-GalN induced ALF. NSA might alleviate ALF via pyroptosis pathway.

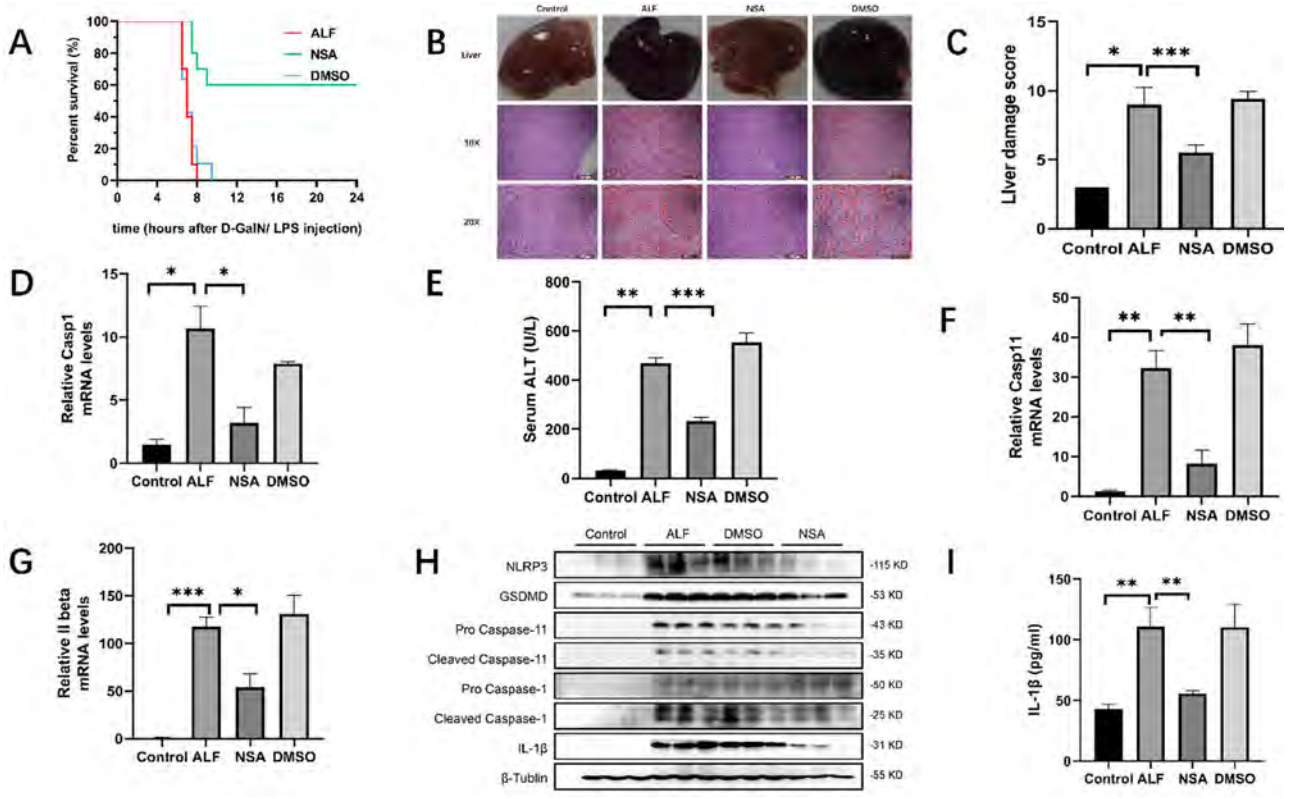

Figure: (abstract: THU188)

Gut microbiota and liver disease

THU189

Administration of lactobacillus alleviates experimental NASH by reducing miR-21 in the liver

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is a widely spread disease mostly associated to the Westernized diet, rich in fat and sugar with strong impact on gut microbiota. The dysbiotic effect contributes to liver disease onset and progression. Recent advances in the study of gut-liver axis have exposed the importance of gut microbiota modulation through the use of probiotics for the treatment of NAFLD. Particularly, *Lactobacillus* species improved liver disease in experimental NALFD. We have shown that miR-21KO mice are protected from gut dysbiosis and liver disease due to increased levels of *Lactobacillus sp.* in an inflammatory mice model. Here, we aim to understand how the therapeutic use of a probiotic strain of *Lactobacillus reuteri* may modulate the expression of mir-21 in the liver and ameliorate non-alcoholic steatohepatitis (NASH) pathogenesis.
Method: Five-month-old male C57BL/6N mice were fed either normal diet or a methionine and choline-deficient diet (MCD) supplemented with 10^9/mL *Lactobacillus reuteri* DSM17938 in sterile water for 8 weeks. Mice were sacrificed, and liver and small intestine recovered for further histological and molecular analyses. Serum was collected for biochemical analyses.
Results: Our results show that therapeutic supplementation with *Lactobacillus* reduced weight loss and ameliorated MCD-induced liver and small intestine damage. In particular, liver histology was improved with less steatosis and inflammation. Consistently, NLRP3, TNF-α, IL-1β and TLR-4 mRNA expression levels were significantly reduced in liver tissue. In small intestine, mRNA expression levels of Lgr-5 and Olfm4 were reduced, while Muc-2, JAM-A and ZO-1 were increased. FXR mRNA was also decreased in the intestine. Importantly, expression levels of miR-21 were reduced in the liver after *Lactobacillus* treatment.
Conclusion: The use of *Lactobacillus* as a preventive strategy in the MCD model of NASH improved gut damage as well as liver steatosis and inflammation via reduced liver mir-21 expression. These results reinforce the importance of the gut-liver axis in protecting the liver.
Supported by PTDC/MED-FAR/29097/2017 and CEECIND/04663/2017 from FCT.

THU190

Disease severity and proton pump inhibitor use impacts strongest on faecal microbiome composition in cirrhosis

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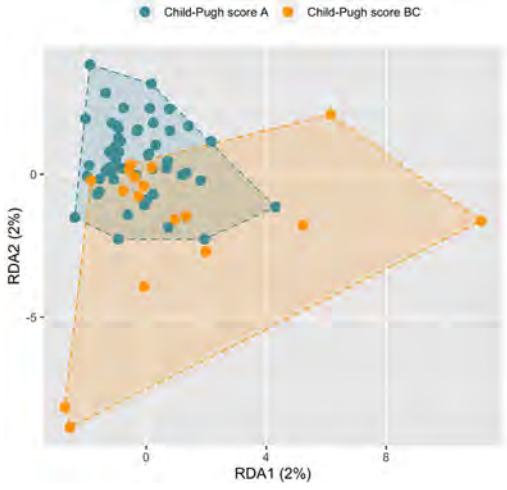
Background and Aims: Compositional changes of the faecal microbiome in cirrhosis are well described and have been associated with complications and prognosis. However, it is less well known, which disease or treatment-related factors affect microbiome composition most distinctively. We aimed to investigate which factors influence microbiome composition in cirrhosis the most by analysing a well characterized cirrhosis cohort with an extensive set of metadata.
Method: 16S rDNA sequencing data of 88 cirrhotic outpatients were investigated. Factors influencing microbiome composition were analysed by univariate and multivariate redundancy analysis. The association of the identified factors with changes in diversity and taxonomic composition was studied in depth using Analysis of Composition of Microbiome, LDA-effect size and Least Absolute Shrinkage and Selection Operator Regularized Regression. Network analysis was performed to understand overlaps of effects.
Results: Disease severity, proton pump inhibitor use, etiology of liver disease, nutritional status, age and C-reactive protein are significant explanatory variables for faecal microbiome composition in liver cirrhosis on redundancy analysis. (Figure). Each of these factors are associated with distinct taxonomic differences. However, since those variables are not entirely independent of each other, the results of taxonomic analyses show large overlaps.
Conclusion: In the analyses and interpretation of descriptive microbiome studies, all possible influencing variables must be taken in account. Especially in chronic diseases, with high morbidity,



Variable	Variance	F-statistic	P-value	Signif.
Severity	16.97	1.25	0.002	**
Aetiology	30.78	1.14	0.004	**
PPI use	15.54	1.15	0.007	**
SGA	16.20	1.20	0.008	**
Age	15.18	1.12	0.041	*
CRP	15.38	1.14	0.050	*
Lac/Man	15.34	1.14	0.096	ns
Bilirubin	14.17	1.05	0.227	ns
Albumin	14.14	1.05	0.238	ns
Lactulose	14.05	1.04	0.255	ns
MELD	13.90	1.03	0.329	ns
PZINR	13.79	1.02	0.382	ns
sMR	13.52	1.00	0.491	ns
Creatinine	13.47	1.00	0.519	ns
Hemoglobin	13.34	0.99	0.567	ns
sCD163	12.81	0.95	0.783	ns

Figure: (abstract: THU190): Redundancy analysis based on Bray-Curtis dissimilarity (PPI: proton pump inhibitor, SGA: subjective global assessment, CRP: C reactive protein, Lac/Man lactulose/mannitol ratio in urine, MELD Model of end stage liver disease, PZINR: International normalized ratio, sMR: soluble mannose receptor, sCD163 soluble CD163).

such as liver cirrhosis, precise patient metadata documentation is of utmost importance. Disease and drug effects are difficult to distinguish. Therefore, detailed analysis of influencing factors on microbiome composition as well as longitudinal studies will allow the identification of potential modifiable factors.

THU191

Patients with alcoholic hepatitis present strong Th1 cellular immune responses to alcohol dehydrogenase related to impairment of the PD-1/PD-L1 pathway due to high circulating levels of soluble PD-1

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Background and aims: Alcoholic hepatitis (AH) is characterised by florid hepatic inflammation, liver failure and high short-term mortality. We have previously reported that AH patients present strong cellular immune responses to alcohol dehydrogenase (ADH), with a predominant Th1 and a limited Th2 response. We have also observed that AH patients have a reduced frequency of suppressive PD-1 expressing CD4 T cells. The imbalanced cellular immune response to ADH is related to a defect in the PD-1/PD-L1 pathway, which negatively regulates T cells and is essential for the maintenance of peripheral tolerance. In this study, I aimed to evaluate the role of circulating soluble PD-1 (sPD-1) in patients with AH.

Method: PBMC and plasma were collected from 29 AH patients (20 female, median age: 43, range 25-63), 12 alcohol-related cirrhosis (ARC) patients (4 female, median age: 61, range 37-74), 9 pathological controls (PC) (NASH, PSC; 4 female, median age: 58, range 39-70), and 14 healthy controls (HC) (6 female, median age: 38.5, range 28-64). $1x10^5$ cells/well were cultured with T cell stimulator and IL-2, with and without 10μM of 8 antigenic ADH peptides. Cells were cultured for 8 days in the presence or absence of anti-PD-1, anti-PD-L1 or combined anti-PD-1/PD-L1 neutralising antibodies. Cells were harvested and FACS used to determine T cell phenotype and frequency of cytokine producing T cells. Duplicate cell cultures were pulsed with 0.25 μCi/well ^{3}H-thymidine for 18 hours and harvested onto glass-fibre lined membranes. Thymidine incorporation was measured using a β-counter and expressed as the stimulatory index (SI). Proliferative responses were positive when SI ≥ 2.5. Plasma (100 μl/well) was used to measure concentrations of soluble PD-1 using a sandwich ELISA according to the manufacturers standard protocol (DuoSet ELISA for human sPD-1, R&D Systems).

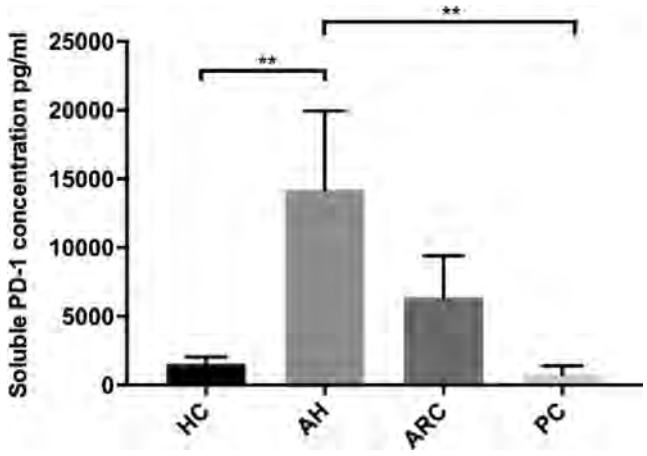

Figure:

Results: In AH, positive PBMC proliferative responses were observed in the presence of ADH peptides, but not in their absence. Frequency of PD-1^{+ve}CD4^{+ve} lymphocytes was significantly higher in the presence of ADH peptides and no PD-1/PD-L1 blockade in HC than in AH (4.40 ± 0.54 versus 1.90 ± 0.26, p=0.003). Mean baseline soluble PD-1 concentration was significantly higher in AH than in HC (14,205 ± 5741 versus 1536 ± 521.4 pg/ml, p=0.0075) and PC (14,205 ± 5741 versus 755.9 ± 658.6 pg/ml, p=0.0032). No other significant differences in sPD-1 were identified between groups.

Conclusion: Soluble PD-1 has been shown to counteract PD-L1 mediated suppression of CD4^{+ve} T cell proliferation in a number of autoimmune diseases. We have identified significantly higher levels of sPD-1 in patients with AH, who demonstrate inappropriate proliferative cellular immune responses to ADH. This may explain some of the beneficial effects of immune suppression in the treatment of AH. Further investigation of the role of sPD-1 is warranted in AH.

THU192

Alteration of the gut microbiota in patients with primary sclerosing cholangitis and concomitant dominant strictures

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Background and Aims: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease often leading to end-stage liver disease. Its pathogenesis remains largely unknown, although frequent concomitant inflammatory bowel disease (IBD) hints towards common factors underlying gut and bile duct inflammation. Considering the mounting evidence on the involvement of the intestinal microbiota in initiating and determining IBD phenotype, we investigated intestinal microbiota composition in patients with PSC and compared it to patients with IBD.

Method: Stool samples of patients with PSC (n = 49) were collected and compared with samples derived from IBD patients (n = 56) during the time period July 2016 till November 2018 at the University Hospital Heidelberg. At the time of collection all patients were in stable clinical condition without overt signs of infection and without antibiotic treatment for at least three months. Samples were prepared for DNA-isolation and sequenced by ILUMINASeq method. In PSC patient subgroups depending on the presence of dominant strictures (DS) or IBD were analyzed. Clinical and laboratory data were collected by chart review.

Results: The alpha-diversity is significantly higher in PSC patients due to a higher richness of the microbiome while the dominance is not significantly different. We also observed a significant change in the structure of the microbiome (R^2 = 2%; p-value: 0.016). This change is due to a significant decrease of Firmicutes and increase of Bacteroides in the PSC group. There was no influence of the underlying IBD on the structure. However, the alpha diversity was significantly increased in patients with PSC only compared to PSC patients with concomitant CU ($p < 0.01$) and CD ($p < 0.05$) indicating a strong effect of the underlying disease on the microbiome. In subgroup analyis of PSC patients with DS we observed no major impact of the stricture on the alpha and beta-diversity level indicating no changes in the overall structure of the microbiome. There was was a slight change in the structure (R^2 = 0.05, p-value = 0.012) and several species showed a significant difference related to the presence of stricture indicating a mild effect on the biosphere of the microbiome.

Conclusion: Gut microbiota composition in PSC patients showes disease specific alterations compared to IBD patients. Differences in the colonic microbiome depending on concomitant IBD or the

presence of DS in PSC might be a contributing factor in PSC pathogenesis.

THU193

Gut microbiota and metabolites associated with response to ursodesoxycholic acid in patients with primary biliary cholangitis

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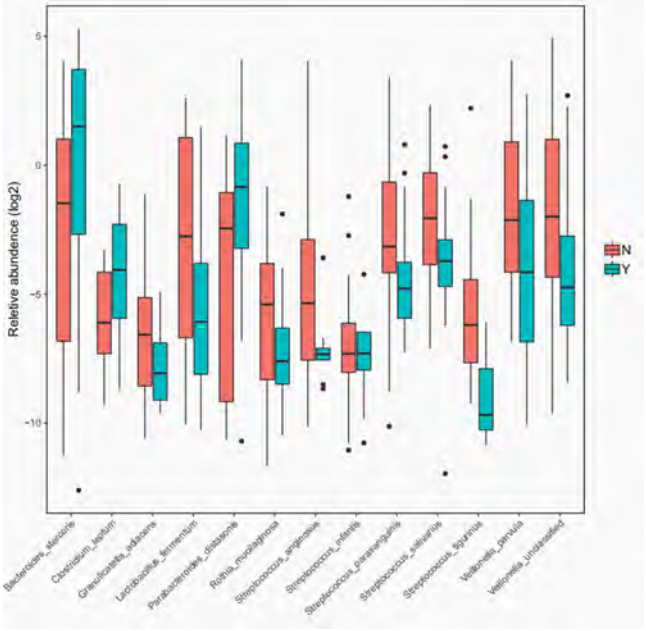
Background and Aims: Ursodeoxycholic acid (UDCA) is the first line drug for primary biliary cholangitis (PBC), which forty precent was inadequate response. The gut microbiota plays an important role in pathogenesis and progress of PBC, but whether affected the responese of UDCA for PBC is unclear,so we compared gut microbiotas and their related metabolites in PBC patients with adequate response and inadequate response after UDCA therapy.
Method: This was a cross-sectional study. According to Paris standard, sixty-one PBC patients were divided to adequate response group (n = 29) and inadequate response group (n = 32). Fecal samples were collected and analyzed by macrogenomic sequencing. Bile acids (BAs) and short chain fatty acid in serum and faeces were measured using UPLC-MS.



Results: The individual diversity (alpha-diversity) of the gut microbiota in UDCA-inadequate patients was no significant change, but the overall microbial diversity (beta-diversity) increased dramatically compared with the UDCA-adequate response (p = 0.009). At the phylum level, the proportion of Firmicutes was higher in the UDCA-inadequate group than that in UDCA-adequate group (p = 0.01). The changes of species level characterized by decreased abundance of three species (Bacteroides_stercoris, Clostridium_leptum and Parabacteroides_distasonis) and increased abundance of ten species (Granulicatella_adiacens, Lactobacillus_fermentum, Rothia_mucilaginosa, Streptococcus anginosus, Streptococcus_infantis, Streptococcus_parasanguinis, Streptococcus_salivarius, Streptococcus_tigurinus, Veillonella_parvula and Veillonella_unclassified) strongly correlated with the effect of UDCA response, the area under curve was 0.838. The fecal BAs of the UCDA-inadequate patients were lower than that in UDCA-adequate patients, but the serum BAs were higher, especially in GCDCA, TUDCA and GUDCA. There was a obvious correlation between the gut microbiota and BAs. In particular, Streptococcusus_tigurinus positively correlated with serum total BAs, GCDCA and TCDCA, and Veillonella_unclassified was negatively related with faeces total secondary BAs and LCA.
Conclusion: The gut microbiome and bile acid metabolism were disordered in the UDCA-inadequate response PBC, which further affected the UDCA efficacy, so altering gut microbiota may a effective approach to improve the response of UDCA for PBC patients.

THU194

Gut microbiota are associated with minimal hepatic encephalopathy (MHE) in cirrhosis regardless of country of origin

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Background and Aims: Cirrhosis is associated with altered gut-brain axis that can predispose to hepatic encephalopathy (HE). Diet, ethnicity and microbiota composition vary, but their impact on different cohorts is unclear. *Aim*: Define differences in gut-brain axis in cirrhosis cohorts from US & Mexico (MX)
Method: Age-matched controls and cirrhotic pts from US & Mexico underwent dietary recall, stool microbiota (16srRNA) analysis and cognitive testing using psychometric hepatic encephalopathy score (PHES, low is better, MHE worse than –4 score). Interactions between microbiota, cognition, and diet in US vs Mexico were compared. Microbial diversity, key taxa and cirrhosis dysbiosis ratio (CDR). CDR is [(Lachno+Rumino+Veillo)/(Enterobact+Bacteroidaceae)]; high ratio indicates lower dysbiosis. Logistic regression for determinants of MHE were performed in the entire group and then only in cirrhosis using cohort origin, diet, demographics, cirrhosis, CDR and other microbiota as variables.
Results: 120 total subjects (60/cohort, 20 controls, 20 compensated & 20 decompensated) were enrolled from tertiary care centers in US & MX. Age and PPI use were similar but there were less men in MX cohort. MELD scores, prior HE (65% each; all on lactulose), MHE were greater & PHES was worse in decomp pts regardless of US/MX.
Diet: MX subjects consumed lower protein and higher carbohydrates vs the US. US subjects consumed more coffee, tea, pork, milk, eggs, cheese and yogurt, and lower fish compared to MX.
Microbiota: Shannon diversity was similar between US/MX. Only MX cohorts had Prevotellaceae with highest in controls and compensated, which reduced in decomp pts; none were found in US. MX pts had higher Enterobacteriaceae, Veillonellaceae, Strep and lower Lactobacillaceae vs US. As expected, advancing cirrhosis had lower beneficial taxa (Lachno, Rumino). CDR was lower in MX decomp vs US decomp pts.
Regression: In the entire group, MHE was associated positively with decomp (OR 3.1, p < 0.001) and negatively with CDR (OR:0.56, p = 0.02). When only cirrhotics were considered, MHE was associated with MELD (OR 1.2,p = 0.04), decomp (OR 4.3, p = 0.05) and cheese (OR 6.9, p = 0.01), while CDR was protective again (OR: 0.6 p = 0.04) independent of cohort, demographics, diet and other clinical factors.
Conclusion: A favorable gut microbial profile (high CDR) is associated with protection from cognitive impairment (MHE) independent of cohort of origin, diet and cirrhosis severity in a multi-center study from USA and Mexico. Efforts to improve dysbiosis could beneficially impact brain function in cirrhosis.

*p<0.05 USA vs MX †p<0.05 within USA ‡ p<0.05 within MX	USA (n=60)			Mexico (n=60)		
	Control (n=20)	Comp (n=20)	Decomp (n=20)	Control (n=20)	Comp (n=20)	Decomp (n=20)
Age	56.8±9.4	59.8±5.7	60.5±6.7	59.9±7.7	55.9±10.9	56.6±10.2
Male*	45%	80%	80%	20%	50%	50%
PHES (high=better)‡†	-0.2±3.2	-1.8±3.6	-5.7±4.9	-0.2±2.0	-1.6±3.2	-3.8±3.5
MHE based on PHES ‡†	0%	15%	60%	0%	20%	45%
MELD score ‡†	-	8.2±2.4	13.7±7.1	-	9.2±2.9	14.1±5.7
PPI use	30%	15%	20%	15%	30%	20%
Diet						
Yogurt*‡†	45%	15%	25%	10%	5%	0%
Milk*	65%	25%	45%	40%	30%	15%
Chocolate*‡	25%	15%	15%	30%	5%	5%
Coffee*‡	55%	70%	65%	55%	30%	20%
Tea*	30%	40%	40%	20%	10%	5%
Cheese*‡	80%	65%	60%	10%	40%	10%
Pork*‡	50%	85%	40%	50%	50%	25%
Beef	90%	90%	65%	95%	80%	75%
Fish*	50%	50%	30%	60%	65%	75%
Eggs*	55%	45%	40%	15%	35%	15%
Cereals*	50%	40%	25%	75%	65%	75%
Microbiota (% relative abundance)						
Bacteroidaceae‡†	27%	33%	18%	27%	14%	35%
Prevotellaceae*‡	0%	0%	0%	14%	43%	3%
Lactobacillaceae*†	0%	1%	3%	0%	0%	0%
Lachnospiraceae*‡†	25%	26%	12%	18%	17%	14%
Ruminococcaceae‡†	12%	10%	4%	15%	10%	6%
Streptococcaceae*‡	0.1%	0.1%	0.1%	0%	0%	1%
Veillonellaceae*‡	0%	0%	0%	0%	2%	2%
Enterobacteriaceae*‡	0%	0%	0%	0%	0%	2%
Shannon diversity‡	1.7±0.4	1.6±0.5	1.6±0.4	1.7±0.2	1.5±0.3	1.4±0.4
Cirrhosis Dysbiosis ratio median(IQR) *‡†	1.1 (2.5)	1.1 (2.5)	0.7 (3.4)	1.3 (1.0)	1.3 (1.0)	0.5 (1.3)

Figure: (abstract: THU194): Characteristics of the Subjects from Both Cohorts.

THU195

Microbiota modulates ischemia-reperfusion injury in mouse liver transplantation

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Background and Aims: Ischemia-reperfusion injury (IRI) is a major risk factor in orthotopic liver transplantation (OLT). As host microbiota may associate with health or disease, antibiotics (Abx) and fecal microbiota transplantation (FMT) can manipulate microbial profile to improve disease status. We have reported on benefits of Abx in IRI-OLT via PGE2/EP4 pathway in mouse and humans. Here, we evaluated the effects of Abx/FMT on taxonomical composition/outcomes in mouse OLT.

Method: In IRI-OLT arm (n = 6/gr), mice (C57BL/6) pretreated±10d amoxicillin (AMPC; 50 g/L in drinking water) were transplanted with 18 h cold-stored liver allografts (Balb/c), followed by OLT/blood sampling (6 h). In FMT group, AMPC-treated recipients received FMT from naïve donors + OLT. In fecal analysis arm, cage-controlled mice were divided into: 1) control, 2) AMPC, 3) AMPC+FMT, 4) OLT groups. To ensure the selective effect of anaerobe bacteria on OLT, metronidazole (MNZ; 1 g/L in drinking water for 10d) was given±FMT (n = 4/gr).

Results: In OLT recipients, AMPC alleviated IRI, evidenced by decreased sALT (3359 ± 1574 vs. 7383 ± 1501 U/L, $p < 0.05$), Suzuki's histological score, frequency of TUNEL+ cells, infiltrating neutrophils/macrophages and enhanced EP4 (IHC). Adjunctive FMT restored hepatic IRI (sALT: 7485 ± 847.6 U/L, $p < 0.05$ vs. AMPC) and reduced EP4 expression. In fecal 16S q-PCR analysis, there were no changes in absolute microbiota levels between groups; while 16S rRNA-amplicon sequencing showed decreased species richness, abundance, and diversity in AMPC vs. control (Faith's, Shannon and Chao1; $p < 0.005$ in each index). FMT abrogated this pattern ($p < 0.005$ vs. AMPC, ns vs. control); and day 1 post-OLT microbiota was comparable with controls. Levels of Akkermansia and Bacteroidetes were increased in AMPC group vs. control; while Ruminococcaceae, Turicibacter, and Clostridium were reduced. Remarkably, MNZ pretreated OLT experienced severe IRI, with increased sALT (8853 ± 353.5 vs. 5486 ± 1345 U/L, $p < 0.05$), Suzuki's score, TUNEL+ cells, and graft-infiltrating neutrophils/macrophages, and decreased EP4 expression vs. controls. FMT adjunct in MNZ-treated OLT restored hepatocellular function to control levels (sALT: 4301 ± 2145 U/L, ns vs. control, $p < 0.05$ vs. MNZ group).

Conclusion: This study documents striking benefits of microbiota modulation in a clinically-relevant mouse OLT model; and identifies a specific microbiota genus profile as a target for novel therapeutic manipulation in IRI-OLT.

THU196

Gut microbiota composition is difference between HCV mono-infection and HCV/HIV co-infection

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Background and Aims: Alteration of gut microbiome has been linked to the pathogenesis of hepatitis C virus (HCV) infection. However, little is known about the effect of human immunodeficiency virus (HIV) infection on gut dysbiosis in HCV/HIV co-infected patients. This study aimed at investigating the difference of gut microbiota composition between patients with chronic HCV mono- and co-infection.
Method: Fecal specimens from patients were collected and extracted for DNA. Gut microbial compositions were analyzed using 16S ribosomal RNA (V3-V4) sequencing by Illumina MiSeq sequencing platform. The alpha and beta diversity were calculated with QIIME pipeline.
Results: This study included 58 patients with HCV mono-infection and 28 patients with HCV/HIV co-infection, who were age and gender-matched. There were no differences in taxonomic diversity (alpha and beta index) and Unifrac-based principle coordinates analysis (PCoA) between groups. The co-infected group showed significantly lower in the relative abundance of genus Faecalibacteria (6.34 ± 5.96 vs. 8.57 ± 6.24, P = 0.043) and Blautia (1.66 ± 1.19 vs. 2.71 ± 2.29, P = 0.044) when compared to the mono-infected group. Patients with cirrhosis showed significant increase in Agathobacter and decrease in Lachnoclostridium when compared to patents without cirrhosis (3.10 ± 3.08 vs. 2.47 ± 5.46, P = 0.043 and 0.60 ± 0.87 vs. 1.15 ± 1.73, P = 0.029, respectively). The abundance of Agathobacter was also increased in patients with F3–4 when compared with patients with F0–2 (3.27 ± 4.35 vs. 2.29 ± 5.34, P = 0.024). In subgroup analysis, Lachnospira was significantly higher in co-infected cirrhotic patients when compared with cirrhotic patients with mono-infection (2.55 ± 1.83 vs. 1.15 ± 1.64, P = 0.012).
Conclusion: This is the first report that compares gut microbiome profiles between patients with HCV mono- and HCV/HIV co-infection. The presence of HIV was accompanied by changes in gut microbiota composition, which might be associated with an increased risk of disease progression in co-infected patients.

THU197

Transplantation of gut microbiota derived from MCJ-KO genotype determines a protective profile against non-alcoholic fatty liver disease in germ-free mice

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Background and Aims: Enhanced activity of mitochondria complex I by deletion of the methylation controlled J (MCJ) protein has proved to avoid liver lipid accumulation. Due to the role of gut microbiota (GM) in non-alcoholic fatty liver disease (NAFLD) development, adaptations induced by MCJ-deficiency could be related to microbiota composition changes. This work aims to evaluate the outcomes of a choline-deficient high-fat diet (CDA-HFD) in MCJ-knockout (KO) mice and to determine if the effects linked to the genotype could be transferred to germ-free mice (GFm).
Method: MCJ-KO and wild type (WT) mice were fed with control (C) diet and CDA-HFD for 6 weeks. Donor mice with a specific metabolic phenotype were selected based on markers related to NAFLD. GFm were colonized with GM from these donors and fed with C and CDA-HFD for 3 weeks. NAFLD activity score (NAS) besides gut-liver axis, fibrosis and inflammation markers were measured.
Results: Mice fed with CDA-HFD showed an increase in fibrosis, inflammation and gut-liver axis alteration parameters. MCJ-KO was related to an improvement of these inflammatory and fibrotic patterns. Based on these results, donors were selected from WT and MCJ-KO mice fed with C and CDA-HFD. CDA-HFD-fed GFm receivers displayed hepatic damage proved by increased plasma transaminases levels, NAS and hepatic triglyceride content. This diet was also associated with enhanced fibrosis, gut-liver axis alteration and hepatic inflammatory response activation. GM transplantation-derived phenotypes evidenced specific functionalities in GFm receivers associated to the donor genotype. CDA-HFD-fed GFm receivers from MCJ-KO donors showed an improvement in signalling pathways related to fibrosis progress, independently of the donor diet. In contrast, only CDA-HFD-fed GFm transplanted with microbiota from CDA-HFD-fed MCJ-KO donor showed a downregulation of inflammatory markers that corresponds with the hepatic histological findings, resulting in a reduced NAS in these receivers. This microbiota profile linked to MCJ-KO genotype and CDA-HFD feeding in GFm triggered an improvement in transaminases and hepatic triglycerides levels.
Conclusion: Our results demonstrate that some beneficial effects of MCJ-KO related to NAFLD development can be transferred by cecal microbiota transplantation, suggesting that GM may be involved in the mechanisms underlying its protective effect. Supported by BFU2017-87960-R and GRS 1888/A/18. CIBERehd is funded by ISCIII. The authors Naroa Goikoetxea-Usandizaga and David Porras and Malu Martínez-Chantar and Sonia Sánchez-Campos equally contributed to this work.

THU198

Effects of anti-TNF? treatment on Crohn's disease induced hepatic steatosis

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Background and Aims: Even in the absence of metabolic risk factors, non-alcoholic fatty liver disease (NAFLD) occurs in up to one-third of patients with inflammatory bowel disease (IBD). To date, little is known about the mechanisms leading to hepatic steatosis in IBD nor how anti-Tumor Necrosis Factor-alpha (anti-TNFα) treatment affects steatosis. However, we and others have shown that NASH in patients with Crohn's disease (CD) is associated with an increased susceptibility for acute-on-chronic liver failure. Multivariate logistic regression analyses have shown that ongoing anti-TNFα therapy was the only independent protective factor. Therefore, we aimed to analyze and compare non-invasive predictors of liver disease paying special

attention to the role of the gut-liver axis and bile-acid (BA) metabolism.
Method: We included patients with established CD with and without anti-TNFα treatment and analyzed serum markers of liver injury, transient elastography as well as controlled attenuation parameter (CAP) and MRI proton density fat fraction to assess hepatic steatosis. Additionally, we analyzed gut microbiota composition and mediators of BA signaling in the absence or presence of treatment with anti-TNFα through analysis of stool and serum.
Results: Patients on anti-TNFα treatment expressed less hepatic steatosis as assessed by CAP and MRI. Serum FGF-19 levels were significantly higher in patients on anti-TNFα treatment and associated with less steatosis as well as lower LFT-levels. Group-specific alterations in gut microbiome were found for several bacteria involved in BA metabolism and FGF-19 regulation, including Bacteroides and Firmicutes.
Conclusion: In this Crohn's disease cohort, anti-TNFα treatment is associated with less steatosis, reduced circulating FGF19 levels, and specific alterations in the composition of gut microbiota and BA metabolism.

THU199
Investigation of microbiome metabolites and mitochondrial function in non-alcoholic fatty liver disease
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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is a hepatic feature of the metabolic syndrome associated with obesity, type 2 diabetes, and increased risk of developing cardiovascular disease (CVD). Intestinal bacteria are increasingly recognised players in metabolic diseases, but it is not yet fully understood how the gut microbiome affects liver function. Trimethylamine N-oxide (TMAO) and phenylacetic acid (PAA) are microbiome-derived metabolites that have been associated with CVD and the early onset of NAFLD, respectively. Hypothesising that these metabolites may contribute to lipid deposition in the liver by altering hepatic mitochondrial function, we are currently assessing how TMAO and PAA affect hepatocyte bioenergetics in cell models of liver steatosis.
Method: HepaRG cells were used because of their ability to differentiate into fully functional hepatocyte-like cells, forming bile canaliculi and presenting CYP450 activity, and potential utility for drug toxicology studies. HepaRG cells were cultured under standard conditions, and steatosis was established by overnight exposure to oleate and palmitate (2:1 molar ratio). Lipid accumulation was quantified by BODIPY™ fluorescence. Mitochondrial bioenergetics were measured in real-time by extracellular flux (XF) analysis in intact control cells and in cells that had been exposed to PAA (100 µM or 200 µM) or TMAO (20 µM, 50 µM, 100 µM and 200 µM).
Results: HepaRG cells responded as expected to bioenergetic effectors as their respiratory activity decreased in the presence of the ATP synthase inhibitor oligomycin, and increased after subsequent addition of a mitochondrial uncoupling agent. These responses demonstrate good coupling efficiency of oxidative phosphorylation and significant spare respiratory capacity. PAA and TMAO lowered spare respiratory capacity dose-dependently in HepaRG cells. Interestingly, removal of these metabolites 48 h post-exposure restored spare respiratory capacity indicating that PAA and TMAO effects are reversible.
Conclusion: Our data indicate that microbiome-derived compounds alter hepatic mitochondrial function and exacerbate lipid deposition. Such effects might suggest that involvement of microbiome-derived compounds with metabolic liver disease is mediated by mitochondrial dysfunction.

THU200
Veillonella as a bile acid-sensitive bacteria and a microbiome-based biomarker for aldafermin (NGM282) in patients with non-alcoholic steatohepatitis
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Background and Aims: Recent studies have shown that the gut microbiome of elite athletes is enriched in *Veillonella*, a performance-enhancing microbe that functions via lactate metabolism (Scheiman et al., Nat Med 2019;25:1104). *Veillonella* is selectively induced in NASH patients treated with aldafermin (previously known as NGM282), a non-tumorigenic FGF19 analogue that significantly inhibits bile acid (BA) synthesis. We hypothesize that *Veillonella* may be a bacteria genus sensitive to BAs. Here we assessed the correlation of *Veillonella* with BA species in a pooled analysis of phase 2 aldafermin trials in NASH.
Method: 144 NASH subjects, with NAS ≥ 4 (at least 1 point in each component), stage 1–3 fibrosis and absolute liver fat content by MRI-PDFF ≥ 8%, received aldafermin 0.3 mg, 1 mg, 3 mg, 6 mg or placebo daily for 12 weeks (W12), and had both baseline (BL) and W12 stool samples collected. Stool microbiota was analyzed using 16S rRNA method (Diversigen). Serum BA was measured with LC/MS (Mayo Clinic). We performed a linear mixed-effect model to account for non-independence of the data set with the following model: *Veillonella*_abundance ~ treatment_type + visit + (1|subject). Correlation between pre- and post-treatment in the relative abundance of *Veillonella* and BA species was determined by Spearman's rank correlation coefficient.
Results: Subjects treated with aldafermin had stable gut microbial composition and diversity. No taxonomic changes were observed among 12 phyla or the top 30 most abundant genera over time or between aldafermin and placebo, except for an increase in the low abundance genus *Veillonella* in subjects who received aldafermin. Enrichment of *Veillonella* from BL to W12 was observed in the aldafermin groups, but not in the placebo group (Figure 1). At W12, the appearance of *Veillonella* was associated with a reduction in BA levels. The relative abundance of *Veillonella* was negatively correlated with concentrations of BAs, and the more hydrophobic, toxic BAs in particular (GDCA: $r = -0.45$, $p < 0.0001$; GCDCA: $r = -0.38$, $p < 0.0001$; DCA: $r = -0.38$, $p < 0.0001$; GCA: $r = -0.37$, $p < 0.0001$).

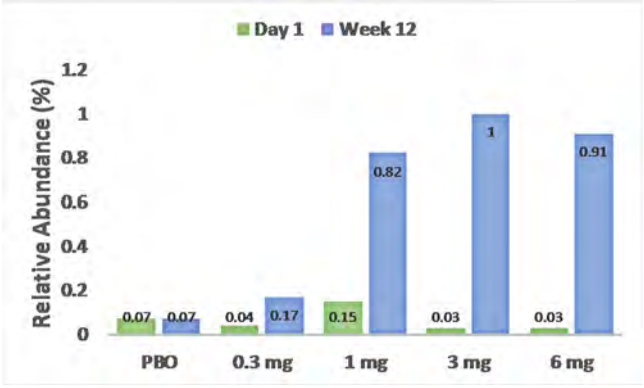

Figure 1: Aldafermin enriches the lactate-consuming *Veillonella* in patients with NASH.

Conclusion: The lactate-fermenting *Veillonella* may serve as a microbiome-based biomarker for aldafermin activity. *Veillonella* appear to be sensitive to BAs, and especially the more hydrophobic, toxic BA species. Given that levels of lactate are elevated in patients with cirrhosis and predict organ failure and mortality, the ability of

aldafermin to enrich lactate-consuming *Veillonella* in the gut could have a protective effect in advanced liver disease.

THU201

Novel metagenomic signature of fungal mycobiome in NAFLD-cirrhosis with validation in a geographically independent cohort

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Background and Aims: Gut bacteria derived metagenomic signature has been associated with NAFLD-Cirrhosis (Caussy et al. 2019 Nature Communications) However, there are limited metagenomic data regarding the role of fungal mycobiome in NAFLD Cirrhosis. The aim was to examine the association between fungal mycobiome in NAFLD Cirrhosis and then validate fungal alteration in an independent racially and geographically distinct cohort of patients from China.
Method: Shotgun metagenomics profiling were performed on stool samples from well-characterized participants ($N = 163$) comprising NAFLD-cirrhosis ($N = 27$) and non-NAFLD controls ($N = 54$) as well as their first-degree relatives or twins. Then, we utilized an independent cohort of Chinese patients with and without cirrhosis (Qin et al. Nature 2014) as a validation cohort.
Results: Using a uniquely phenotyped cohort of NAFLD-cirrhosis ($N = 27$) and non-NAFLD controls ($N = 54$), we identified significant alteration of microbial fungi. We found *Saccharomycetaceae* was significantly enriched and uniquely associated with NAFLD-cirrhosis at the family level. Our metagenomic analysis enabled to identify that subclass of *Saccharomycetaceae, Candia glabrata,* was increased in NAFLD-cirrhosis at species level (mean 3.57-fold up). Furthermore, we identify that a unique strain of *Candia glabrata* highly enriched in NAFLD-cirrhosis is *GCA 000002545*. In order to identify common or unique fungi signatures, we utilized 237 participants (114 controls and 123 cirrhosis) from Chinese cohort and examined change of fungal composition. Importantly, we observed *Saccharomycetaceae* was consistently enriched in cirrhotic samples from the Chinese cohort. Surprisingly, *Candia glabrata* (strain: *GCA 000002545*) was also consistently more enriched in Chinese cirrhotic samples (Wilcox $P < 0.0057$). Notably, we found a unique alteration that *Saccharomyces cerevisiae* was the most enriched in Chinese cirrhosis samples (Wilcox $P < 0.01$). Meanwhile, we found *Candia glabrata* is the most significant enrichment in the UCSD cohort, suggesting *Candia glabrata* is a potential biomarker for NAFLD-cirrhosis.
Conclusion: We have identified significant alteration of fungal composition that accurately represents liver NAFLD-cirrhosis, consistent with enteric dysbiosis observed in disease progression. The utility of this pattern change (e.g. *Saccharomycetaceae* [family], *Candia glabrata* [species], *GCA 000002545* [strain]) is demonstrated as it is also altered in cirrhotic samples from a Chinese cohort. This external validation is unique to cirrhosis since previous studies have mainly focused on bacterial profiling and alteration of fungi has not been demonstrated or validated using a geographically independent cohort. Further studies are needed to better understand the pathogenetic role of these alterations in fungal mycobiome in cirrhosis and its complications.

THU202

Lactobacillus rhamnosus GG improve fungal dysbiosis on liver cirrhotic rats

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Background and Aims: Cirrhotic patients are susceptible to fungal infection with high mortality. While infected cirrhotics have bacterial dysbiosis, the role of fungi is unclear. Gut microbiota regulation are considered a potential treatment strategy to protect liver injury. This study aimed to evaluate the functional role of *Lactobacillus rhamnosus* GG (LGG) in fungal structure and liver inflammation on cirrhotic models
Method: Thirty-eight SD rats were randomly divided into healthy control (NC group, $n = 8$) and experimental groups ($n = 15$). Each group was administrated with LGG or normal saline once daily during the induction of liver cirrhosis by CCl_4. Subcutaneous injection of 50% (V/V) CCl4 solution in olive oil was used to induce liver cirrhosis at a dose of 2 ml/kg twice a week for 13 weeks. A PC group treated with normal saline during cirrhosis induction as positive control ($n = 15$). Animals were euthanised one week after the last injection of CCl_4 solution, with liver tissue and caecal contents taken for the subsequent biochemical and molecular analyses.
Results: Rats in PC group displayed an unfavourable intestinal fungal signature, mainly in the increase of common pathogenic fungi, and the reduction of symbiotic and beneficial fungi. Compared with healthy control group, at the family level, the abundance in the PC group was significantly reduced in the yeast family *Saccharomycetaceae* and *Trichomeriaceae*. At the genus level, the abundance of PC group was significantly increased by *Candida* and *Zygosaccharomyces*, and *Nakaseomyces* and *Knufia* were significantly decreased in NC group. LGG administration could increase the fungal diversity and change the intestinal fungal structure during cirrhosis induction. The structure of intestinal fungi in LGG group was similar to that of normal group flora, and the population difference between the groups was small. Compared with the PC group, at the genus level, the LGG group significantly reduced *Candida* and increased the abundance of *Nakaseomyces*. At the species level, the LGG group significantly reduced *Candida. Catenulata* and significantly increased *Candida. glabrata* abundance. LGG treatment significantly reduced the translocation of fungal β-glucan into systemic circulation and attenuated liver inflammation, which was correlated with the decreased abundance of *Candida.*
Conclusion: There is a significant fungal dysbiosis in cirrhotic rats. LGG can improve the intestinal fungal structure of cirrhosis, reduce the proliferation of pathogenic fungi, and ameliorate liver inflammation. Probiotics intervention suggest novel strategies for the prevention of fungal infection in liver cirrhosis.

THU203

Protective effects of akkermansia muciniphila against non-alcoholic fatty liver disease through modulation of gut microbiota

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Background and Aims: There exists gut microbiota dysbiosis in NAFLD (Nonalcoholic Fatty Liver Disease), and the imbalance may be related to stages of liver injury. However, the dynamic changes of intestinal flora during the development of NAFLD are still poorly understood. Akkermansia muciniphila can regulate host's immune

and metabolic functions. This study intends to use a high-fat diet-induced NAFLD mouse model and explore the effects of Akkermansia muciniphila on NAFLD as well as its underlying mechanisms.
Method: C57BL/6 mice were fed with high-fat diet for five months to induce nonalcoholic fatty liver disease. During the experiment, mice were either administered with 3 * 10^9 CFU of Akkermansia muciniphila by oral gavage every day or given the same amount of PBS. We measured the intestinal barrier function, metabolic biomarkers, liver injury, inflammation, lipid metabolism, and gut-liver FXR-FGF15 axis. Besides, the alteration of intestinal bile acids and gut microbiota was also measured.
Results: Akkermansia muciniphila reduced HFD-induced weight gain, improved insulin resistance and glucose tolerance, and alleviated liver injury. Akkermansia muciniphila significantly inhibited the hypertrophy of visceral fat, improved dysbiosis of the metabolic factors like leptin and resistin, and reduced the uptake of fatty acids and triglyceride deposition of liver. Akkermansia muciniphila maintained the gut barrier function and reduced endotoxin translocation. In addition, the up-regulation of gut-liver FXR-FGF15 axis inhibited the expression of CYP7A1 in the liver. The structure of intestinal microbiota changed during the development of NAFLD which was improved by Akkermansia muciniphila.
Conclusion: This study found that Akkermansia muciniphila has a protective effect on NAFLD induced by high-fat diet. It can inhibit intestinal barrier permeability and endotoxin translocation, reduce abnormal synthesis of adipokines, and regulate the balance of gut bile acids and the intestinal FXR-FGF15 axis. These effects may be related to the significant modulation of intestinal microbiota by Akkermansia muciniphila.

THU204
Identification of gut bacterial candidates involved in hepatic encephalopathy by the analysis of feces DNA from patients administered rifaximin

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Background and Aims: The gut microbial dysbiosis has been discussed as a cause of hepatic encephalopathy (HE) where hyperammonemia is one of the major causes of the disease. However, the key gut microbial species that could cause the pathophysiology of HE remain to be elucidated. Therefore, our research focused on identifying gut bacterial species that functionally causing the pathophysiology of HE, based on the analysis of the gut microbiota profile of HE patients' feces DNA before and after RFX administration.
Method: From April 2017, we consulted 26 patients with liver cirrhosis who had been administered with RFX (1200 mg/day). In 19 of 26 cases, we analyzed the blood ammonia levels as well as gut microbial profile before and every two weeks after RFX administration, and categorized the patients as effective (n = 10) and non-effective cases (n = 9) judging by the reduction level of blood ammonia. We performed 1) the comparison of the gut microbiota profile using 16SrRNA gene sequence analysis and LEfSe (Linear discriminant analysis effect size) before and after RFX administration, 2) the oral administration of the identified gut bacterial species in CCl_4 treated cirrhosis mouse models to see the enhancement of blood ammonia levels, and 3) the isolation of bacteria which could contribute to HE pathophysiology from fecal samples derived from the non-effective cases.
Results: 1) Clear differences were detected in the gut bacterial profile between the two groups. LEfSe analysis identified the candidate bacterial species that were significantly abundant in the effective cases as ammonia-producing bacteria, and the amount of bacteria decreased with RFX administration. 2) Significant enhancement of blood NH_3 levels was observed ($p = 0.049$) in mice with oral administration of the candidate bacterial species, confirming the relationship between this bacterial species and hyper-ammonemia in mouse models. 3) RFX-resistant bacteria, that were highly competent to produce ammonia, were successfully isolated from the feces of non-effective patients.
Conclusion: We identified strong candidates of bacterial species involved in the pathophysiology of HE.

Liver development, physiology and regeneration

THU205
Modulation of native decellularized liver matrix enhances hepatic cells proliferation, viability and functions on 3D-bioscaffolds

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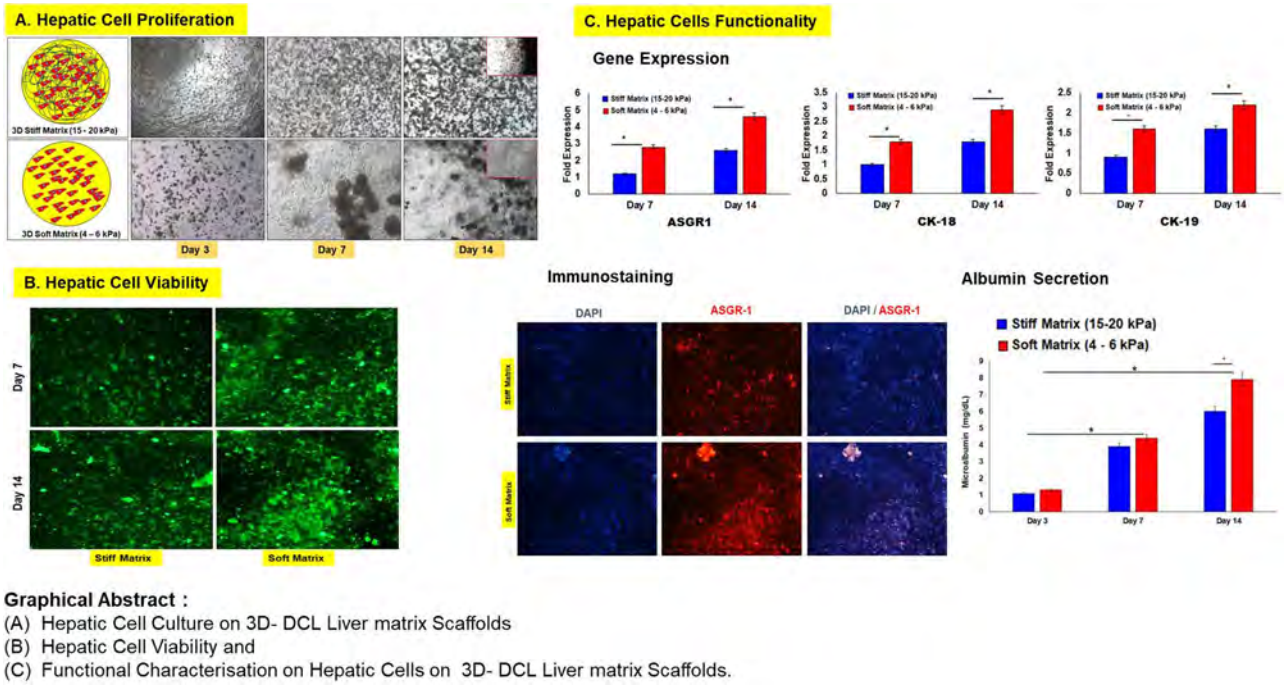
Background and Aims: The Extracellular matrix (ECM) provides various physicochemical cue in directing cells behaviour, proliferation and functions. Liver stiffness acts as a vital cue affecting liver regeneration and repair. 3D In-vitro models that mimic the liver stiffness corresponding to various stages of disease progression might help to elucidate the role of cellular responses. Here, we developed 3D-bioscaffolds with solubilized decellularized liver (DCL) containing matrices with tunable mechanical properties and investigated the effect of substrate stiffness on the behaviour of hepatic cells.
Method: DCL was developed by portal vein cannulation and perfusion with detergents and characterized by histology and DNA content. Enzymatically digested DCL matrix was mixed with commercially available hydrogel to create 3D-bioscaffolds. To recreate physiologically relevant stiffness, we designed soft (4–6 kPa) to represent the healthy liver and stiff (15–20 kPa) liver matrix by mixing of varied DCL matrix concentration with hydrogel. Hepatic cells were cultured on stiff and soft 3D scaffolds till 14 days. Phenotypic and functional analysis was done by cell morphology, cell viability, hepatic gene expression, immunostaining and albumin secretion at day 3, 7 and 14 of cultured hepatic cells.
Results: DCL histology and DNA content (less than 50 ng/ml) confirmed the intact matrix and complete removal of hepatic cells from the native liver. More than 90% hepatic cells viability was observed in cultured conditions. However, at day 14, proliferation of hepatic cells was significantly increased on 3D-soft bioscaffolds than stiff ($p < 0.05$). Gene expression of hepatocyte specific markers, Asialoglycoprotein Receptor 1(ASGR-1), Cytokeratins CK-18 and 19 was increased more than 2 and 4 folds at day 7 and 14 in 3D- soft scaffolds than stiff ($p < 0.05$). Liver-specific (ASGR-1) immunostaining also showed significantly enhanced expression in 3D-soft scaffolds at day14 than the stiff ($p < 0.05$). Secretory albumin levels from hepatic cells were significantly increased in the culture supernatants at day 7 and 14 in 3D-soft bioscaffolds ($p < 0.05$).
Conclusion: Our results showed that 3D bioscaffolds supports enhanced hepatic cell viability and functionality. Mechanical factors in 3D-liver bioscaffolds have important implications for understanding the development and progression of liver disease and for new drug screening.



Graphical Abstract :
(A) Hepatic Cell Culture on 3D- DCL Liver matrix Scaffolds
(B) Hepatic Cell Viability and
(C) Functional Characterisation on Hepatic Cells on 3D- DCL Liver matrix Scaffolds.

Figure: (abstract: THU205)

THU206

Hepatocyte-targeted R-spondin mimetic for liver regeneration

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Background and Aims: Wnt signaling plays a central role in hepatocyte expansion during development and tissue repair. R-spondins (RSPOs) amplify Wnt signaling via stabilization of Frizzled and LRP co-receptors and their function depends on the presence of Wnt ligands, which are upregulated in injured tissue. A major limitation to the potential therapeutic use of Wnts and RSPOs is their widespread effect on several organs, and in liver, on non-hepatocyte cells. To leverage the Wnt regenerative potential for parenchymal mass expansion, we generated a hepatocyte-targeted antibody-based R-spondin mimetic. We named this molecule, SWEETS-1, for Surrozen Wnt Enhancer Engineered for Tissue Specificity.
Method: *In vitro*, Wnt signaling activity was measured using the Huh-7 hepatic or HEK293 non-hepatic cell lines containing a luciferase gene controlled by a Wnt-responsive promoter (Super Top Flash reporter assay, STF). *In vivo*, SWEETS-1 (0.01–30 mg/kg), RSPO (0.01–10 mg/kg) or the negative control anti-beta-galactosidase (0.01–10 mg/kg) were injected intraperitoneally. Liver samples were collected 48 hours later for gene expression analysis of the Wnt target gene, Axin2, and for immunofluorescence analysis with the proliferation marker, Ki67 and the hepatocyte differentiation marker, HNF4-alpha. To examine the tissue-specific activity of SWEETS-1, expression of Axin2, was measured by qPCR in kidney, salivary gland, intestine, heart, lung, pancreas, skin and spleen.
Results: SWEETS-1 enhanced Wnt signaling in the Huh-7 hepatic cell line to a level similar to that of RSPO. In contrast to RSPO, which induced Wnt signaling in the Huh-7 hepatic and HEK293 non-hepatic cell lines, SWEETS-1 activity was limited to Huh-7 cells. SWEETS-1 enhanced the expression of the Wnt target gene, Axin 2, to a level similar to that of RSPO. In contrast to RSPO which induced Wnt signaling in kidney, salivary gland, intestine, heart and pancreas, SWEETS-1 induced Axin2 expression in liver only. Immunofluorescence analysis revealed that SWEETS-1 induced Ki67 positive nuclei specifically in HNF4-alpha-hepatocytes.
Conclusion: These results show that SWEETS-1 can stimulate hepatocyte-specific cell regeneration. This approach may be beneficial for the treatment of liver diseases.

THU207

Primed liver regeneration in protein convertase subtilisin/kexin type 9 knockout mice is associated with increased lipids uptake and hypercholesterolemia

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Background and Aims: Liver regeneration is a complex and well-orchestrated process following partial hepatectomy (PH). Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) has an important role in the regulation of plasma low-density lipoprotein cholesterol (LDLc) levels by shuttling liver LDL receptors (LDLR) for degradation, which in fact mediates hepatic clearance of LDLc from the circulation. Transient hepatic steatosis following PH indicates a functional relationship between lipid metabolism and hepatocyte proliferation, all phenomena not well defined yet. Herein, we studied the regenerative potential of PCSK9 knockout (KO) mice after PH in order to determine the functional significance of PCSK9 in the context of hepatic lipid metabolism during liver regeneration.
Method: A single-cell RNA sequencing (scRNA-seq) database of murine liver cells isolated following a standard two-thirds PH was examined for gene expression analysis. LDLR expression, Oil Red O-stained hepatic lipid droplets accumulation and lipid parameters in the serum were deeply analyzed after PH, as well as hepatocyte proliferation and liver regeneration capability in PCSK9 KO and control mice.

Results: scRNA-seq data showed that PCSK9 was mainly expressed in cholangiocytes and hepatocytes, where exclusively in the latter its expression was regulated by PH. mRNA and protein expression levels of LDLR were increased in PCSK9 KO mice before PH and after liver resection. Greater intrahepatic transient lipid droplets accumulation and lower cholesterolemia were observed in the KO animals compared to the controls, with a markedly reduced cholesterol biosynthesis rate (3-Hydroxy-3-Methylglutaryl-CoA Reductase – HMGCR gene expression). There were no histological alterations in liver morphology and architecture between the two groups, whereas an increased liver/body weight ratio together with a higher proliferation index and pro-proliferative genes upregulation were observed 30–36 h after PH in PCSK9 KO mice.
Conclusion: We observed increased hepatocellular cholesterol uptake and enhanced liver regeneration in PCSK9 KO mice. The increase of LDLR expression as well as the higher transient liver steatosis and hypocholesterolemia seem to be crucial factors and events in priming the compensatory hyperplasia of the liver after PH.

THU208

Targeting the embryonic liver with ultrasound-guided in utero nano-injection to manipulate gene expression during liver development and hematopoiesis

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Background and Aims: In order to understand developmental principles in liver, gain of function, loss of function, and lineage tracing studies in vivo are undertaken to decipher gene function during stem cell proliferation, commitment, and differentiation. Manipulation of gene expression in liver cells typically relies on liver-specific cre-drivers (eg AFP-cre) or AAV specific to liver cell types (eg AAV8 for hepatocytes). However, traditional mouse genetics approaches are slow and expensive, while AAV approaches are more rapid, but limited by viral tropism. Furthermore, the fetal liver is home to both future liver cells (hepatocytes and cholangiocytes), as well as the future hematopoietic system. We therefore aimed to develop a technique to rapidly and flexibly manipulate gene expression in fetal liver stem cells and hematopoietic stem cells (HSCs).
Method: We adapted ultrasound-guided in utero nano-injection to achieve gene manipulation in embryonic liver (Fig 1). To determine the optimal parameters to target liver cells and HSCs, we tested different injection volumes, viral titers, injection sites, and developmental stages. Developmental stages tested include E7.5 (exocoelomic cavity), E10.5 (liver bud) and E13.5 (liver). Analysis of targeted cells is performed by qPCR, scRNA seq, FACS, and immunocytochemistry/immunohistochemistry on liver sections.

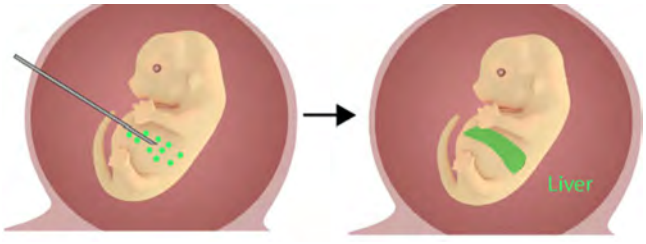

Figure: Ultrasound-guided nano-injection with GFP-encoding lentivirus (or cDNA/shRNA/sgRNA of interest) to target the liver.

Results: In utero nano-injection with GFP-encoding lentivirus results in successful viral integration in embryonic liver cells and HSCs, allowing gain of function, loss of function or lineage tracing. GFP+ cells are detectable in liver as early as E10.5, and can be detected in blood cells at postnatal stages.
Conclusion: Ultrasound-guided in utero nano-injection is a feasible, powerful method to investigate gene functions in liver development and hematopoiesis. It requires fewer mice, is faster and cheaper compared to using genetically engineered mice. With the help of this technique, we are now investigating gene function in liver and hematopoietic development.

THU209

Development and automation of 3D innovative hiPSC-based liver organoids including the microenvironment for phenotyping screening - application on metabolic diseases

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Background and Aims: We previously showed that urine-derived human pluripotent stem cells (hiPSCs) provide a suitable model to study metabolic diseases, such as familial hypercholesterolemia, upon hepatocyte-like cell (HLC) differentiation. While the direct link between hiPSCs and patients, as well as the abundance of HLCs provide promising advantages, it is impaired by the neonatal characteristic of HLCs and the difficulty to perform high-throughput studies for pharmacological investigations.
To overcome these burdens, we chose to 1. Design a 3D hiPSCs differentiation procedure to enhance their maturation. 2. Adapt our setup to a 96-well format compatible for drug screening.
Method: To reach our goals, we established a partnership with HCS Pharma, which produces an innovative 3D hydroscaffold, BIOMIMESYS®, composed of modified Hyaluronic Acid that can be biofunctionalized with extracellular matrix derivatives, with adjustable stiffness and porosity.
Results: Our strategy allowed us to generate liver organoïds in a 96-well plate format, through a unique and common procedure, without separated cell culture mixed thereafter. We performed a global gene expression analysis throughout their differentiation, and a head-to-head comparison between 2D and 3D showing an enhanced expression of most hepatic genes and non-parenchymal cells such as stellate cells. Immunofluorescence data confirmed, among others, the co-localization of albumin-positive hepatocytes, desmin-positive stellate cells and LYVE1 positive sinusoidal endothelial cells in liver organoids. At the functional level, liver organoids showed several CYP activities including CYP3A4, at the basal level and increased upon induction, the ability to accumulated lipids upon amiodarone or ethanol treatment and to activate stellate cells into myofibroblasts.
Conclusion: We can produce patient-specific metabolically functional liver organoids in Biomimesys™ in a format adapted for molecular screening and/or metabolic target identification.

THU210

Dynamic characterization of revascularization in decellularized whole-liver scaffold

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Background and Aims: Vascular reconstruction of decellularized whole-liver scaffold is a major challenge for in vivo transplantation of functional recellularized whole-liver. We aimed to reendothelialize whole-liver scaffold, and characterize the biological process to evaluate degrees of revascularization.
Method: We reendothelialized the scaffold with 1.5×10^7 human umbilical vein endothelial cells (HUVECs), followed by 3 weeks of continuous perfusion using the self-developed bioreactor. Native, decellularized and reendothelialized (days 1, 3, 7, 14 and 21) livers were collected for histological analysis and further proteomic analysis with LC-MS/MS technique. Functional enrichment analysis was performed with the DAVID database.
Results: HUVECs were gradually migrated and adhered to form an endothelium after reendothelialization. Dynamic histological analysis on reendothelialized samples harvested at days 1, 3, 7, 14 and 21 shown revascularization process. Revascularization reduced blood leakage and platelet adhesion upon blood perfusion. The positive staining with VE-cadherin further confirmed the integrity of endothelial barrier. Principal component analysis shown that the samples of day 14 and 21 are significantly different from those at other time points. Proteomic analysis shown that numbers of human-derived proteins were gradually increased from day 1 and synthesized extracellular matrix (ECM) proteins participated in ECM reorganization. 114 proteins, mainly participate in the process of cell adhesion, protein synthesis and energy metabolism, were always expressed in the process of three-week revascularization. Compared with day 1, proteins associated with the regulation of vasoconstriction were significantly differentially expressed at day 14 and 21. Three differential proteins (MYBPC, MYH1 and alpha-SMA), associated with cytoskeleton regulation and cell phenotype transition, were validated by immunohistochemistry.

Conclusion: This study successfully achieved the reendothelialization of whole-liver scaffold for up to 3 weeks. Further proteomic analysis revealed that stable and mature vessels were formed after two-week culture. Overall, revascularization dynamic characteristics will better promote transplantation of functional recellularized whole-liver.

THU211

Optimal liver metabolism and proliferation require the tight junction protein claudin-3

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Background and Aims: The expression of hepatic tight junction proteins and their contribution to homeostasis and regeneration remained largely unexplored. Here, we determine the cell type specific expression of tight junction genes in murine livers. We further explore the regulation and functional importance of the transmembrane protein CLDN3 in normal and regenerating livers.

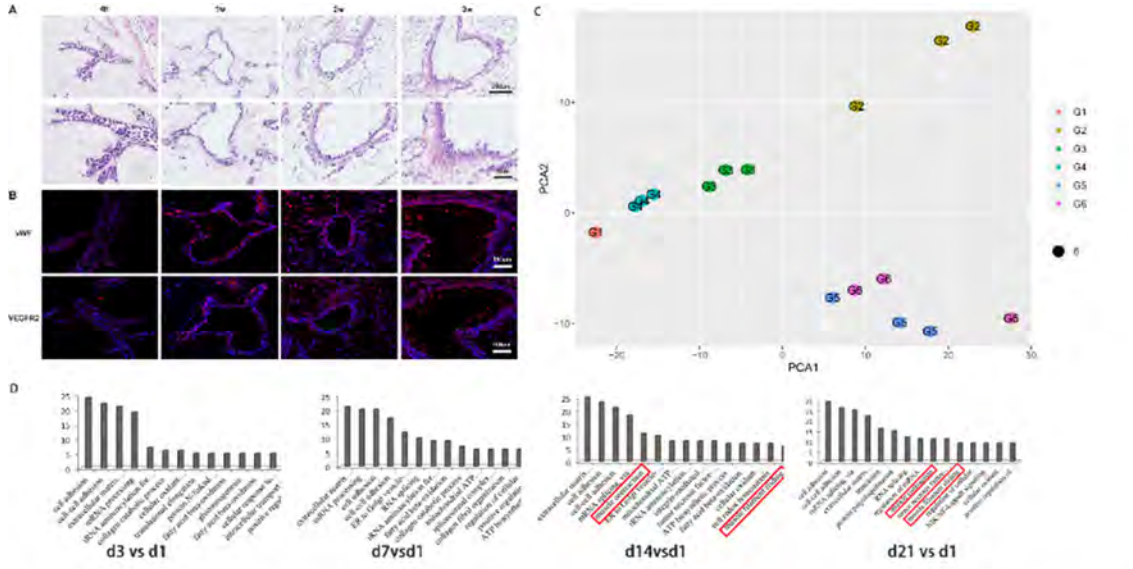

Figure1: Results of re-vasculaturation in vitro and dynamic proteomic analyses. (A) H&E staining of re-vascularization in different phases. (B) Immunofluorescence staining of markers of endothelial cell ,vWF and VEGFR 2. (C) Principal omponent analysis G2-G6 respectively represent d1,3,7,14,21.. (D)Go Ontology enrichment analyses on different

Figure: (abstract: THU210)

Method: Murine livers were used for tissue- and single cell RNA-seq. CLDN3 localization was determined by immunofluorescence. CLDN3 +/+ or CLDN3−/− livers were analysed by electron microscopy, fluorescence-activated cell sorting and liquid chromatography mass spectrometry. Lipid content was quantified with oil-red. Mice were subjected to 2/3 partial hepatectomy. Proliferation was quantified with Ki67 and pHH3 stainings. Cell cycle gene expression was determined by RT-qPCR. Barrier impairments were assessed with total bile acid measurements. Differential gene expression was analysed by tissue RNAseq with DESeq2.
Results: We determined the profile of tight junction gene expression in the main liver cell types, showing that tight junction transcripts can be found in hepatocytes and cholangiocytes but also on non-parenchymal cell populations. CLDN3 was among the highly expressed- and regulated genes in native and regenerating livers. CLDN3 had a zonated expression pattern. CLDN3−/− mice had microscopically intact tight junctions, but showed significantly downregulated hepatic energy metabolism and suboptimal cell proliferation in the regeneration model.
Conclusion: Our data suggests a functional role of CLDN3 for maintenance of energy homeostasis and optimal regeneration, proving that the function of hepatic tight junction proteins extends beyond basic membrane sealing.

THU213

Serum transferrin levels reflect hepatocyte nuclear factor 4 alpha activity in the liver

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Background and Aims: Decreased serum transferrin (TF) levels constitute an independent predictor of short term mortality in patients with alcoholic hepatitis (AH), decompensated liver cirrhosis and acute-on-chronic liver failure (ACLF). The aim of this study was to evaluate the pathomechanisms underlying the prognostic usefulness of serum transferrin in individuals with chronic liver disease.
Method: Factors regulating transferrin expression were assessed via transcriptomic and methylomic analysis in human livers with/without severe AH (sAH). The biological relevance of identified candidates was tested in primary mouse hepatocytes. An *in silico* analysis of transcriptomic data from alcoholic cirrhosis liver specimen was complemented by assessment of dual serum-mRNA samples from 33 patients with chronic liver disease of different etiologies.
Results: Hepatic transcriptome analysis of sAH samples revealed a strong positive relationship of *TF* with the nuclear factor *HNF4a* ($r = 0.74$, $p < 0.0001$) and negative associations with the cytokines TGFb1, TNFa, IL1b, and IL6. Hypermethylation of the *TF* gene in patients with sAH appears to be of regulatory importance. In primary hepatocytes, treatment with TGFb1 or the HNF4a inhibitor BI6015 suppressed *TF* production, while exposure to TNFa, IL1b, and IL6 had no effect. *In silico* data demonstrated a correlation between *TF* and *HNF4a* mRNA levels in patients with alcoholic cirrhosis. In patients with different chronic liver diseases, serum TF levels moderately correlated with hepatic *TF* ($r = 0.51$, $p = 0.004$). Immunohistochemical und biochemical analysis confirmed reduced HNF4a and TF protein levels in individuals with liver cirrhosis.

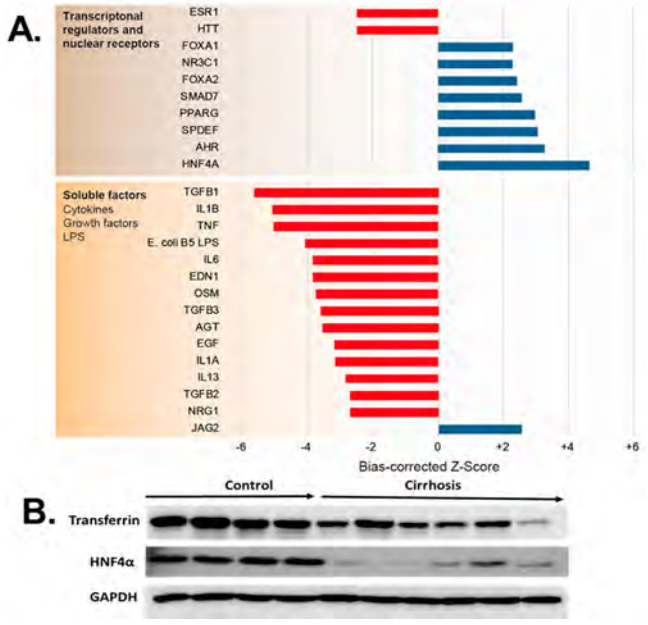

Figure: **Regulation of transferrin production in human liver disease.** (A) Ingenuity Pathway Analysis was used to identify factors predicted to control the Transferrin-correlated transcriptome in individuals with alcoholic hepatitis (B) immunoblotting was used to determine transferrin and HNF4α levels in patients with and without alcoholic cirrhosis. GAPDH was used as a loading control.

Conclusion: Decreased TF serum levels indicate impaired intrahepatic *HNF4a* signaling and may therefore predict the development of hepatocellular failure.

THU214

Macrophage regulation of PKM2 during liver regeneration process

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Background and Aims: The pyruvate kinases (PKs) are responsible for the last and limiting step of the glycolytic pathway. Four PKs proteins, PKL, PKR, PKM1, and PKM2, are differentially expressed depending on cell type and metabolic need, with PKL being the hepatocyte-specific PK. PKM2 is expressed in proliferative cells such as cancer cells and stem cells, as well as immune cells. In macrophages, the polymerization state dictating the nuclear or cytoplasmic localization of PKM2 has been shown to change depending on their polarization. The tetrameric protein complex is enzymatically active in the cytoplasm, and the nuclear dimeric complex acts as a transcriptional activator via binding to HIF1a, promoting proinflammatory cytokine production.
Method: Liver regeneration was induced by 60% partial hepatectomy and inhibited using shikonin or adenovirus delivered shPKM2. PKs expression was evaluated by qPCR, single-cell RNA-Seq, mass cytometry, and immunostaining. Isolated human hepatocytes were exposed to recombinant PKM2 was produced in bacteria and isolated by affinity chromatography.

Results: Analysis of PKs expression during liver regeneration, revealed a decrease of PKL and a parallel increase of PKM2 as early as 3 h post-PH and sustained through the regenerative process up to 7 days. Interestingly, PKM2 inhibition by shikonin or shPKM2 resulted in a decrease in liver regeneration markers. The identification of PKM2 expressing cells revealed that PKM2 was increased in the bone marrow-derived macrophage but not in the Kupffer cells. The PKM2 polymerization state was change between 12 h and 24 h post-PH (also observable in the serum), which was accompanied by a macrophage polarization shift.
Careful examination of PKM2 immuno-staining and mass cytometry showed that pericentral hepatocytes have a moderate level of cytoplasmic PKM2. This increased PKM2 at 3 h and 6 h post-PH proved the presence of PKM2 protein besides the lack of hepatocyte PKM2 RNA expression. In vitro, we could show that hepatocytes can uptake recombinant PKM2 suggesting the possible macrophage origin of the hepatocyte PKM2.
Conclusion: PKM2 is increased in macrophages shortly after PH and is necessary for liver regeneration. The evolution of the macrophage polarization during liver regeneration coincides with a shift in PKM2 polymerization. Finally, the release of PKM2 in the extracellular space may allow its uptake by hepatocyte, suggesting compensation mechanism for the loss of PKL activity.

THU216
Diploid hepatocytes drive physiological liver renewal in adult humans

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Background and Aims: The liver is an organ with an enormous regenerative capacity and current studies aim to understand this extraordinary property. Specific aspects of hepatocyte renewal in humans remain unclear, as the direct exploration of these processes is difficult due to methodological restrictions. Detailed knowledge about the age distribution of human hepatocytes and the dynamics of hepatocyte renewal is still lacking.
Method: We used retrospective radiocarbon (^{14}C) birth dating to establish the age of hepatocytes in healthy, adult humans. This technique utilizes the incorporation of nuclear-bomb-test-derived ^{14}C into genomic DNA to quantify cellular ages. A mathematical model was built, using a kinetic equation that accounts for cell division, cell death as well as changes in ploidy, to characterize human hepatocyte turnover from experimental ^{14}C data.
Results: To establish the dynamics of cell renewal in the human liver with ^{14}C birth dating we analyzed liver tissues from n = 32 healthy subjects aged 20–82 years. Our observations indicate that hepatocytes are renewed throughout adulthood and that there is no evidence for a quiescent population in homeostasis. Instead, by analyzing the different ploidy classes in the human liver, we found diploid hepatocytes to show a turnover rate of 45% per year and an average life-span of one year in mid-aged individuals. On the contrary, hepatocytes of higher ploidy classes display much slower turnover dynamics of seven per cent per year and live around eight years. These findings support the view that in contrast to rodents, the physiological liver renewal in humans is mainly dependent on diploid hepatocytes, whereas polyploid cells are compromised in their ability to divide. Moreover, polyploid hepatocytes do not frequently reverse to a diploid state under homeostatic conditions.
Conclusion: In our study, we utilize ^{14}C dating to provide a new integrated model of hepatocyte generation in humans that gives fundamental insights on their turnover dynamics. We show that the age distribution of human hepatocytes is highly dependent on the ploidy level, which increases substantially with aging. Our data indicate that age-related liver diseases might at least partly be related to impaired hepatocyte renewal in polyploid hepatocytes.

THU217
Imaging human liver regeneration by multiphoton microscopy

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Background and Aims: The combination of mouse models and intravital microscopy has provided unique insight into liver disease pathogenesis. However, mouse models do not accurately represent human inflammatory disease pathogenesis. We aimed to adapt methods commonly associated with intravital microscopy to image live human liver disease tissue ex vivo, to study liver regeneration in the context of drug discovery.
Method: Using 3D-printing, we developed *in situ* perfusion systems and fluorescence labelling strategies which reproducibly permit the imaging of live human tissue using multiphoton microscopy (MPM). We have access to tissue from over 250 liver transplants a year at the Queen Elizabeth hospital, Birmingham, UK. In both non-cirrhotic donor livers and end stage disease explants, we assessed tissue viability using reporters of mitochondrial membrane potential, enzymatic activity and endocytosis. We identified regions of collagen-rich fibrosis using second harmonic generation (SHG). Finally, we observed cellular responses in the tissue in response to acute injury by cauterisation.
Results: Sinusoidal and parenchymal architecture was identified in *ex vivo* liver tissues using MPM and commercially available contrast dyes. These tissues displayed evidence of viability and regeneration up to 48 hr following perfusion. We could track the migration of infused fluorescence-labelled leukocytes within the tissue in three dimensions to a depth of >100 µm. We documented areas of necrosis, regeneration, and hepatocyte phagocytosis proximal to cauterisation injury.
Conclusion: Our methodology provides a new platform to study authentic human liver disease; it permits the observation of regeneration in response to injury, as well as the assessment of pharmacological compounds, in real time.

THU218
Thyroid hormone and TGF-? inhibition drive functional maturation of human pluripotent stem cell-derived hepatocytes

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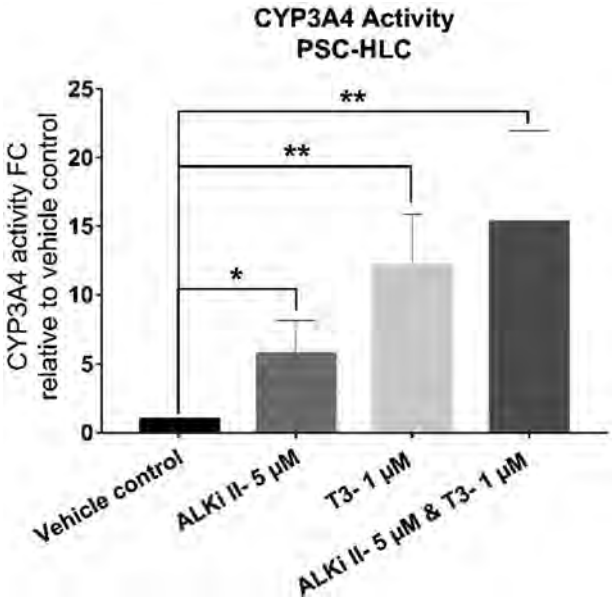
Background and Aims: The usefulness of pluripotent stem cell-derived hepatocytes (HLC) for modeling hepatotoxicity, human disease, or therapy depends on their ability to recapitulate the many functions of the adult liver. This includes expression of nuclear receptors, transcription factors and activity of the adult-specific cytochrome P450 (CYP450) enzymes which metabolize xenobiotics. We have previously demonstrated by transcriptome, proteome, and functional analyses that current HLCs from multiple labs are most similar to fetal rather than adult liver, hindering their use as a reliable hepatocyte cell model. We aimed to identify and target gene pathways that would advance hepatic maturation in iPSC derived HLCs.

Method: We undertook RNA-sequencing of HLCs throughout differentiation and compared their transcriptomes to human adult liver, fetal liver and multiple other human fetal tissues. We used differential gene expression and advanced pathway analysis tools to identify key sub-optimally expressed transcription factor networks in HLC which we hypothesized were limiting their ability to functionally mature. We identified and screened a number of small molecules predicted to target these suboptimal networks to successfully advance hepatic maturation. Quantitative PCR, Western blot, albumin secretion and CYP3A4 enzyme expression (luciferase detection) were used to measure maturation state.

Results: We identified HNF4A and CEBPA as limiting factors in hepatic maturation. Their expression and that of their multiple downstream targets is sub-optimally expressed in HLC, at levels most similar to fetal liver. We further predicted TGF-β overexpression in HLCs was inhibiting HNF4A. We therefore treated differentiating cells with thyroid hormone (T3) and ALK5i II (TGF-β receptor inhibitor) to significantly increase CEBPA and HNF4A expression, respectively, and confirmed this by QPCR and Western blot. On average, combined treatment increased hepatic gene expression (including ALB, A1AT, CYP3A4, CYP2C9, CYP2C19 and CYP3A7) by 10 to over 100-fold compared to published protocols. CYP3A4 enzyme activity increased by 15-fold on average. We also detected significant increases in Albumin secretion. We confirmed that the maturation promoting effects of these treatments were reproducible across multiple cell lines and with multiple common HLC differentiation protocols.



Conclusion: HNF4A and CEBPA transcriptional networks are sub-optimally expressed in HLCs. TGF-β signaling is over-represented in PSC-derived HLC generated by multiple labs. Treatment of HLC with T3 and ALK5i II during the differentiation protocol promotes significant increases in both transcription factors and their downstream targets. CYP450 gene expression and activity is restored to values more similar to adult liver.

THU219

Nicotinamide riboside promotes liver regeneration by enhancing mitochondrial fatty acid oxidation

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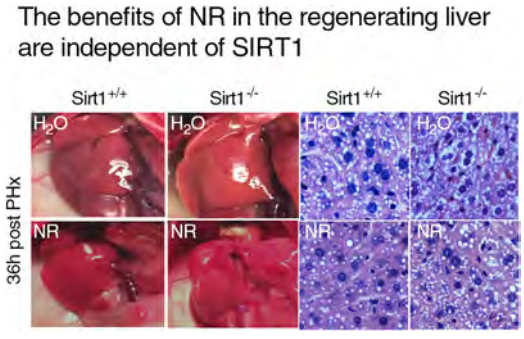
Background and Aims: The regenerative capacity of the liver is essential for the replacement of hepatocytes that are lost due to injuries, surgical resection, or chronic disease processes. Nicotinamide adenine dinucleotide (NAD) levels markedly decline during liver regeneration, which may result from metabolic competition for common precursors required for DNA synthesis. We have previously showed that augmenting NAD synthesis, either genetically or by supplementing with the precursor nicotinamide riboside (NR), is sufficient to accelerate liver regeneration in mice. However, the underlying mechanisms have remained unclear. NAD deficiency in the injured liver could plausibly slow regeneration through direct effects on metabolism and bioenergetics, or indirectly through changes in the activity of the signaling enzymes such as Sirtuins. Here, we aimed to understand the molecular mechanisms underlying this improved liver regeneration.

Method: We examined the effects of NR supplementation on mitochondrial function and respiratory capacity in isolated hepatocytes and in isolated mitochondria. We employed genetic models of liver-specific deletion of Sirtuin 1 (SIRT1) and mitochondrial Sirtuin 3 (SIRT3), both NAD-dependent enzymes that have been implicated in liver regeneration and fatty acid oxidation.

Results: NR treatment enhanced the fatty acid oxidation capacity of mitochondria isolated from regenerating livers and increased circulating levels of ketone bodies, suggesting increased beta oxidation of fatty acids *in vivo*. Deletion of hepatic SIRT1 or SIRT3 impaired liver regeneration, however NR supplementation still improved regeneration in these models. Treating primary hepatocytes with NR for 5 hours was sufficient to increase fatty acid oxidation, glucose output, and production of beta-hydroxybutyrate, demonstrating that NR rapidly increases anabolic capacity.



Conclusion: Increasing NAD concentration fuels anabolic processes in hepatocytes by promoting mitochondrial oxidation of endogenous lipid stores in a SIRT1 and SIRT3-independent manner. Improved respiratory capacity is observed even in isolated mitochondria. Our data support a direct metabolic role of NAD in promoting

mitochondrial fatty acid oxidation from lipid substrates during liver regeneration. Thus, providing supplemental NAD precursors and lipid substrates may be effective strategies to promote recovery from liver injuries.

THU220

Potential role of two novel agonists of thyroid hormone receptor-beta on liver regeneration

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Background and Aims: Although the hepatomitogenic activity of 3,5,3'-triiodothyronine (T3) is well established, the wide range of harmful effects exerted by this hormone precludes its use in regenerative therapy. The aim of this study was to investigate whether two novel agonists of thyroid hormone receptor-beta (TRbeta), the prodrug TG68 and the active compound IS25, could exert a mitogenic effect in the liver in the absence of T3/TRalpha-dependent side effects.
Method: Three different doses of both compounds (12.5, 25 and 50 mcg/100 g body weight) dissolved in drinking water were given to F-344 male rats for 1 week. Activation of TRbeta was assessed by qRT-PCR. The proliferative effect was measured by immunohistochemistry, qRT-PCR and western blot.
Results: The results showed that, at all the employed doses, both drugs displayed a significant increase in bromodeoxyuridine incorporation (from 14 to 28% vs. 5% of controls), which was associated with increased mitotic activity. Hepatocyte proliferation was preceded by up-regulation of *Dio1* and *Spot14*, two classical TRbeta target genes. No significant signs of liver toxicity, as showed by lack of increased serum transaminase levels, was observed following the administration of IS25 and TG68. No change in the serum levels of free fraction of thyroid hormones was detected after treatment with the two agonists. Noteworthy, while cardiac hypertrophy typical of T3 was not observed, beneficial effects, such as lowering blood triglyceride levels, were associated to TG68 administration. Importantly, no proliferation of pancreatic acinar cells, such as that observed after T3 treatment, was detected, suggesting the hepato-specificity of these novel TRbeta agonists.
Conclusion: Here we show that TG68 and IS25 induce hepatocyte proliferation without obvious toxicity. Hence these agents may be useful for regenerative therapies in liver transplantation or other surgical settings.

Liver transplantation and hepatobiliary surgery: Clinical aspects

THU221

Parenchyma-sparing hepatectomy improves salvageability and survival for solitary small intrahepatic cholangiocarcinoma

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Background and Aims: Previous study has reported comparable survival outcomes and increased perioperative morbidity for major hepatectomy in comparison to minor resection for intrahepatic cholangiocarcinoma (ICC). However, their conclusion was draw on patients with heterogeneous tumor characteristics, for part of which major resection was inevitable due to large tumor size. This study aimed to investigate the prognostic impact of parenchyma-sparing hepatectomy (PSH) on solitary small ICC.
Method: A total of 184 patients who underwent hepatectomy for solitary small ICC (≤5 cm in size) from 2009 to 2017 were identified. Short- and long-term outcomes were compared between PSH and Non-PSH approach.
Results: 95 (51.6%) patients underwent PSH and 89 (48.4%) patients underwent Non-PSH for solitary small ICC. Baseline tumor characteristics were comparable between two groups. PSH was associated with less intraoperative blood loss (212.9 mL versus 363.5 mL, p = 0.038), lower transfusion rate (7.4% versus 16.9%, P = 0.048), without increasing the frequency of tumor recurrence (60.0% versus 58.4%). No significant differences were observed in overall survival (OS), recurrence-free survival (RFS) and liver RFS (p = 0.627, 0.769 and 0.538, respectively). 109 (59.2%) patients experienced recurrence, of them, 67 (36.4%) were intrahepatic recurrence. Subgroup analysis of patients with liver-only recurrence demonstrated an increased opportunity of repeat hepatectomy for PSH compared to Non-PSH (21.2% versus 2.9%, p = 0.031), thus resulting in improved liver OS (p = 0.016). Multivariate analysis identified PSH approach and repeat resection for recurrent lesion as independent favor factors for liver OS.
Conclusion: PSH was associated with improved perioperative outcomes while did not increase liver recurrence in comparison to Non-PSH. PSH offered an increased rate of salvage hepatectomy for recurrent tumor, thus improving long-term survival in case experienced liver recurrence.

THU222

Reducing length of stay in patients following a liver transplant

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Background:

- There are seven liver transplant centers in Canada, however, data on length of stay (LOS) has not been analyzed in any center.
- Some United States transplant centers have suggested a target of 18 days.
- Prolonged LOS in hospital can result in increased rates of infection, malnutrition, and increased healthcare resource utilization thus a multidisciplinary effort to reduce LOS may improve patient outcomes and reduce costs.
- London health Sciences Centre had a median LOS of 18 days from January 2015–August 2017.

Aims:

1. The aim of the current project was to reduce the median LOS by 3 days over a 16-month period.

Method: Improvement:

2. We used the model for continuous improvement and instituted four Plan-Do-Study-Act (PDSA) cycles to achieve our aim.
3. The 1st PDSA cycle (n = 23) included educational sessions among liver transplant team members.
4. The 2nd PDSA cycle (n = 9) included development of a liver transplant clinical pathway.
5. The 3rd PDSA cycle included institution of a clinical order set (n = 14).

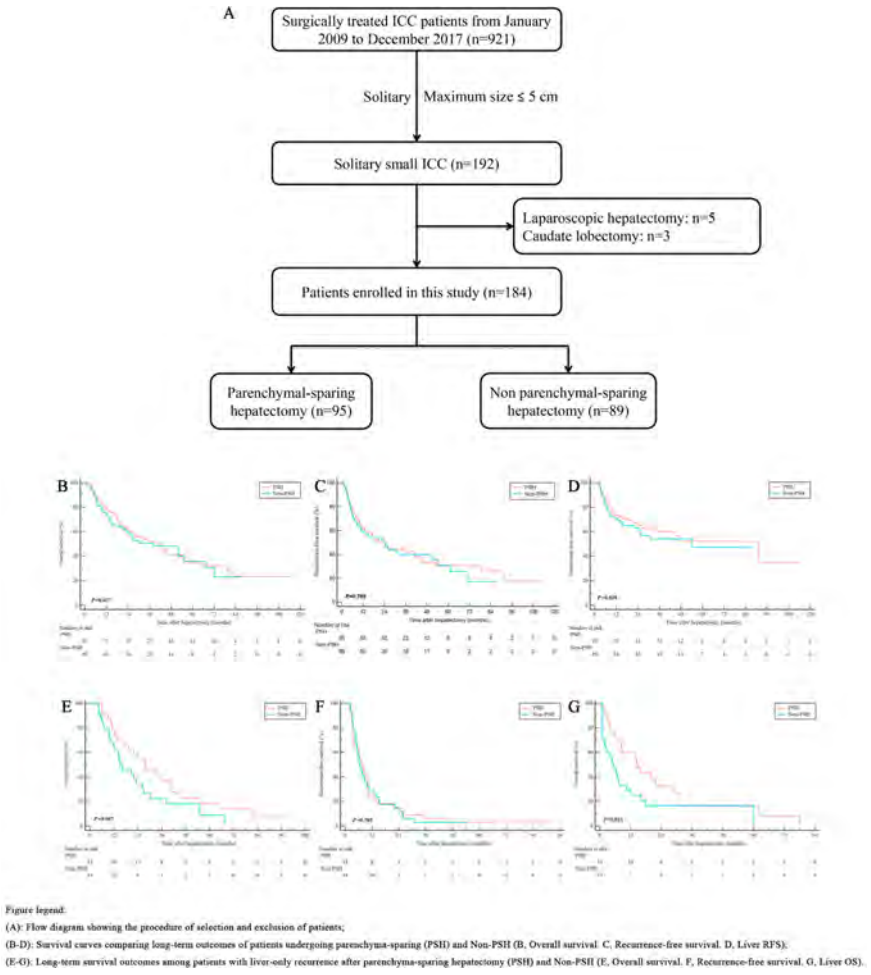

Figure legend:
(A): Flow diagram showing the procedure of selection and exclusion of patients;
(B-D): Survival curves comparing long-term outcomes of patients undergoing parenchyma-sparing (PSH) and Non-PSH (B, Overall survival. C, Recurrence-free survival. D, Liver RFS);
(E-G): Long-term survival outcomes among patients with liver-only recurrence after parenchyma-sparing hepatectomy (PSH) and Non-PSH (E, Overall survival. F, Recurrence-free survival. G, Liver OS).

Figure: (abstract: THU221)

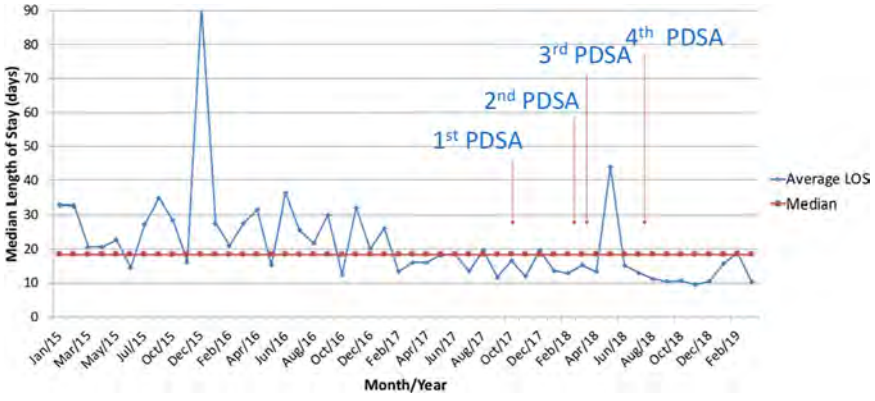

Figure: (abstract: THU222): Run chart rules satisfied over the study period as more than six points were below the median and there was also a trend for more than five consecutive points of improvement.

6. The 4th PDSA cycle (n = 19) involved a patient oriented clinical pathway instrument.

Information gathered/Approach Taken

6. The study took place at University Hospital in London, Ontario from August 2018 – February 2019.
7. 1st PDSA – awareness/education among healthcare professionals.
8. 2nd PDSA – Initiate clinical pathway for patients and healthcare professionals to follow (if applicable).
9. 3rd PDSA – Initiate HUGO Care Set to help facilitate mandatory orders and transfers from ICU.
10. 4th PDSA – Clinical pathway individualized to the patient placed in patient rooms.

Results: Current Status of Project/Project Impact:

6. Over a 16-month period we had 49 liver transplants discharged from hospital with a median LOS of 10 days.

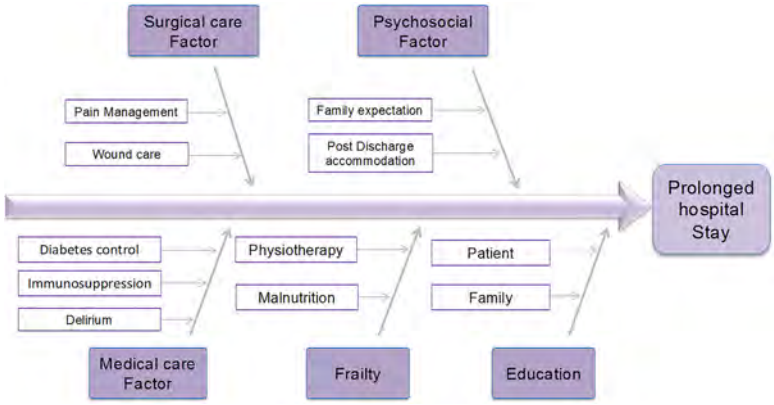

Figure: (abstract: THU222): Ishikawa diagram showing factors relating to Prolonged Hospital Stay.

7. We also analyzed balancing measures and found 30 day and 90 readmission rates to be 18.4% and 22.4%, respectively, which was not significantly different from the 2015–2017 rates of 15.4% and 22.7%.
8. Over this brief study period, $540,000 hospital dollars were saved, which is put toward the global hospital budget.

Conclusion: Development of a multidisciplinary care pathway with patient engagement led to improved discharge rates within a target of ten days.

- Balancing measure of increased readmission rates were not clinically significant.
- During the project period we found further areas of intervention that were preventing patient discharges within target times:
  a. Education/Managing patient expectations
  b. Psychosocial/family support
  c. Frailty (lack of rehabilitation homes/hospital transfer facilities)
  d. Discharge planning
- Macro hospital level issues will be a future barrier to further improvement.

THU223

The presence and outcome of biliary sphincter disorders in liver transplant recipients according to the Rome IV classification

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Background and Aims: Biliary sphincter disorders after liver transplantation (LT) are poorly described. The aim of this analysis was to describe the presence and outcome of patients with papillary stenosis (PS) and functional biliary sphincter disorders (FBSD) after LT, according to the updated Rome IV criteria (Cotton et al. Gastroenterology 2016; 150:1420–29).
Methods: We reviewed all endoscopic retrograde cholangiopancreatographies (ERCP) performed in LT recipients with duct-to-duct biliary anastomosis from 01/2003 to 01/2018. Information on clinical and endoscopic findings was obtained from electronic health records and endoscopy databases. Laboratory and clinical findings were collected at the time of ERCP and 1-month after ERCP.
Results: 1162 patients underwent LT between 01/2003 and 01/2018. 271 LT recipients underwent 691 ERC's during this time period. Twenty patients met the updated Rome IV criteria for PS (former sphincter of Oddi dysfunction (SOD type I) (20/1162, 1.7%). Twelve patients (1.03%) met the Rome IV criteria for FBSD (former SOD type II). Biliary sphincterotomy was performed in 20 (PS group) and 8/12 (FBSD group) respectively. One month after sphincterotomy, bilirubin, ALP and GGT levels decreased in 60%, 70% and 45% of patients respectively in the PS group and in 42%, 58% and 42% of patients respectively in the FBSD group. Thirty-five percent (7/20) of patients with PS had an additional diagnosis on top of PS during follow-up whereas all of the patients initially suspected of having a FBSD group turned out to have a different diagnosis after the ERCP.
Conclusion: PS alone or in combination with other diagnosis can account for a small proportion (1.7%) of LT recipients undergoing ERCP due to cholestasis. Our data does not support the existence of a FBSD after LT. Sphincterotomy is a safe and effective procedure in LT recipients with PS.

THU224

Impact of sarcopenia in patients awaiting simultaneous liver and kidney transplantation: a cohort of study on clinical outcomes

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Background and Aims: Little is known on the impact of sarcopenia in patients undergoing simultaneous liver and kidney transplantation (SLKT). The aim of this single center cohort study was to focus on sarcopenia impact on SLKT recipient's clinical outcomes: patients and grafts survival, infections and complications free-survival at 6 and 12 months.
Methods: Between 2003 and 2018, 79 consecutive patients underwent to SLKT at Pitié Salpêtrière department. Sarcopenia was assessed only in 43 patients through the total psoas muscle area (TPA) at the level of the 3rd lumbar vertebra, measured on a CT scan realized either during the pre-SLKT workup (up to 4 months before SLKT) or in the first 7 days following transplantation. Sarcopenia was defined by TPA <1460 mm^2 in women and <1560 mm^2 in men. Post-operative

complications included biliary and vascular complications. A survival analysis was performed by Kaplan Mayer method with log rank test.
Results: We included 43 SLKT recipients (56% male, median age of 58 (53–63) years). The liver disease was cirrhosis in 74% (n = 32) with a median MELD-score of 21 (20–22), and polycystic liver disease in 26% (n = 11) of patients. Unknown end-stage renal disease was observed in 12 36.2% (n = 12) of patients, with 54,8% (n = 23) of them requiring dialysis before transplantation. Median TPA was 1138 (926–1510) mm^2, and sarcopenia was observed in 72% patients (n = 31). No difference was observed in 6 and 12 months patients or grafts survival censored for death in sarcopenia-group vs. non-sarcopenia-group (overall p = 0.76; liver graft p = 0.8; kidney graft p = 0.83, respectively). Six months post-operative complications free survival was not significantly different in the sarcopenia vs. non-sarcopenia-group respectively, 50% (95%CI: 0.284–0.880) vs. 53%, (95%CI: 0.3791–0.745), (p = 0.61). No difference in infection free survival was observed between two groups at 6 months: 52% (95%CI: 0.213–0.787) vs. 65% (95%CI: 0.4643–0.536), (p = 0.088).
Conclusions: In this cohort of patients, no difference was observed among patients, grafts, complications or infection-free survival among SLKT sarcopenic or none patients. Future studies including more patients are needed to confirm and clarify these results.

THU225

Recent trends and intention-to-treat survival of liver transplantation for non-alcoholic steatohepatitis: an Italian liver transplant registry study. On behalf of AISF, FIRE, SITO and CNT

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Background and Aims: A recent European Liver Transplant registry study showed that the proportion of liver transplants performed for nonalcoholic steatohepatitis (NASH) in Europe has increased from 2002 through 2016, and that the post-transplant outcome in patients with NASH is comparable to that of other disease indications. There are few data on recent trends in waiting list inscriptions/dynamics, and on intention-to-treat transplant survival of NASH patients, however.
Method: We analysed data from adult patients listed for primary LT for chronic end-stage liver disease between January 2012 and December 2018 using the Italian Liver Transplant Registry database. We evaluated annual trends of waiting list inscriptions according to main liver disease aetiologies. Moreover, we compared data of patients with NASH with that of other aetiologies in terms of patient characteristics and intention-to-treat survival outcome.
Results: Among 8,567 adults listed for first LT in Italy in the study period, 494 (5.8%) had NASH. The proportion of NASH patients significantly increased from 3.6% in 2012, to 8.9% in 2018 (p < 0.001). The proportion of patients with alcohol related–liver disease similarly increased from 11.6% in 2012, to 19.2% in 2018 (p < 0.001). Conversely, the proportion of hepatitis C patients significantly decreased from 46.8% to 33.5% (p < 0.001), while that of hepatitis B patients remained stable during the study period around 13%.
NASH patients were older than no-NASH patients (59 vs. 55 years, p < 0.001), and more often had associated hepatocellular carcinoma (51% vs. 45%, p = 0.005). The 1-, 3- and 5-year intention-to-treat survival rates were 81%, 70% and 65% in the no-NASH group vs. 74%, 64% and 56% in the NASH group, p = 0.004. The presence of NASH was a significant risk factor for death (hazard ratio [HR] 1.30; 95% CI 1.07–1.56) also at multivariable Cox survival analysis.

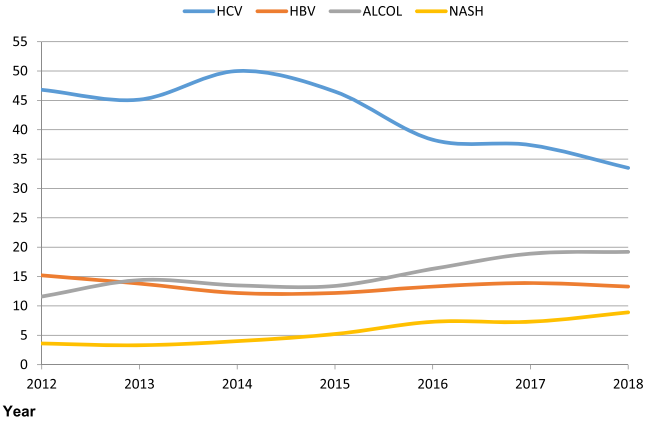

Figure 1: Recent trends of waiting list inscriptions for LT in Italy according to main liver disease etiologies.
Conclusion: The proportion of NASH patients listed for LT in Italy has significantly increased from 2012 to 2018. This preliminary analysis suggests a significant negative impact of NASH aetiology on intention-to-treat transplant survival.

THU226

The application of immunoglobulins after liver transplantation influences the occurrence of donor-specific antibody associated complications

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Background and Aims: Human immunoglobulins (IGs) are used after liver transplantation (LT) e.g. for hepatitis B recurrence prophylaxis and for therapy of cytomegalovirus infection. In addition to their primary function, an overarching immunomodulatory function may have further effects on the course of the disease after transplantation. The occurrence of donor-specific antibodies (DSA) plays a pathophysiological role after solid organ transplantation and leads to complications such as transplant rejection. Subject of this study is the investigation of a relation between the application of human immunoglobulins (Hepatect, Zutectra, Cytotect) and the occurrence of DSA or associated complications after LT.
Method: The DSA status, as well as further clinical and laboratory chemical data after LT were retrospectively collected from 427 patients and statistically evaluated. Detection of DSA was performed by lymphocyte toxicity test and antibody specification by Luminex® technology. Data was statistically analysed by Fisher-Exact test and Chi-square test.
Results: In the cohort, 15.5% of the patients (n = 66) received immunoglobulins after LT. In the course after IG application, 13 of these patients (19.7%) became DSA positive. Of the 361 patients who did not receive IG, 18% developed DSA (P < = 0.864). Regardless of IG administration, complications occurred in both groups in approximately 74% of patients (P < = 0.887). The overall occurrence of complications was neither with nor without IG administration dependent on the DSA status (P > 0.5). However, there was a reduced risk of graft rejection after IG administration, regardless of DSA status (n = 6/66; 9% versus n = 50/361; 14%; P < = 0.424). In addition, patients with IG application had a significantly lower risk of

developing DSA-associated *de novo* autoimmune hepatitis (*de novo* AIH) after LT (P < = 0.043).
Conclusion: The application of immunoglobulins after LT appears to reduce the risk of transplant rejection regardless of DSA status. Likewise, the risk for DSA-associated *de novo* AIH is significantly reduced. An extension of the evaluations will provide further insights into the influence of human immunoglobulins in the long-term course after liver transplantation.

THU227

A new score including anthropometric measurement for weight improved prediction of mortality in adolescents on the liver transplantation waiting list: a US nationwide study

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Background and Aims: The Model for End-Stage Liver Disease (MELD) was adopted for liver transplant (LT) allocation to adolescents with chronic liver disease (CLD) without published validation in children. Pediatric CLD is associated with poor growth that may affect implementing MELD in adolescent patients. Therefore, we assessed the performance of MELD, MELD Na, and the Pediatric End-Stage Liver Disease (PELD) score in predicting adolescent LT wait list mortality. In addition, we evaluated incorporating height and weight into MELD at the time of registration to improve the prediction of mortality in listed adolescents for LT.
Method: Adolescents (12–17 years of age) registered for their first LT in the United States between January 2003 and December 2015 were identified using the united network for organ sharing (UNOS) database. Patients listed for multiple organs, Status 1A or 1B, and those who were granted exception points, were excluded from the analysis. Area under receiver operating curve (AUROC) and C-statistics were used to evaluate the discrimination of MELD, MELD Na, and PELD for the prediction of wait list mortality at 6 and 12 months. Weight, height, and their Z scores at time of registration were examined by univariate analysis and later incorporated into a multivariate regression analysis to obtain a new model termed Adolescent PELD.
Results: A total of 946 adolescent patients fulfilled our eligibility criteria. The cohort was randomized into derivation (n = 473) and validation cohorts (n = 473). Both cohorts had similar age (median 15 for both, p = 0.56), sex (female, 54% vs. 52%, p = 0.27), weight (56 vs. 57 kg, p = 0.52), and height (161 vs. 160 cm, p = 0.66), respectively. Z scores for weight, height, and laboratory variables (Na, creatinine, INR, bilirubin) were similar between cohorts. Median follow-up was 6 months (IQR 1–21) for both cohorts. Overall 100 patients (11%) died while waiting for LT (50 in each cohort), while 437 patients (46%) had LT (209 in derivation cohort and 228 in validation cohort). Only Z score for weight was a significant predictor in univariate and multivariate analysis to predict 6 month mortality on the LT waitlist. Therefore, we created a new prediction model incorporating Z score for weight with MELD score (Adolescent MELD). In the derivation cohort, Adolescent MELD performed better than PELD, MELD, and MELD Na to predict 12 month mortality (AUROC: 0.78 [0.71–0.86], 0.67 [0.59–0.75], 0.74 [0.66–0.83], and 0.75 [0.65–0.84]; p < 0.05 for all comparisons, respectively). Similarly, Adolescent MELD performed significantly better than the other scores in predicting 6 month and 12 month mortality in our validation cohort.
Conclusion: Incorporating the anthropometric measurement Z score for weight improved the accuracy of MELD and the prediction of mortality on the LT waiting list.

THU228

Post-transplant lymphoproliferative disease after adult liver transplantation has a higher incidence after primary sclerosing cholangitis and can be prevented by surveillance of Epstein-Barr viral load with a pre-emptive strategy - a long-term study

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Background and Aims: Epstein-Barr virus (EBV) primary infection or reactivation can occur after liver transplantation (LT). An infrequent but serious complication after LT is post transplant lymphoproliferative disease (PTLD). In paediatric LT recipients -with more primary infection- it has been reported that peripheral blood EBV-DNA surveillance in the first year after LT, with a pre-emptive strategy in case of positivity including reduction of immunosuppression (IS), has led to a lower incidence of PTLD. For adult LT recipients, with less primary EBV infection and a lower PTLD incidence, the value of EBV surveillance is unknown. The aim of this two-centre study was to examine the impact of a strategy based on EBV-DNA monitoring on the incidence of PTLD in adult LT recipients, comparing both a contemporary and a historic control group without EBV-DNA surveillance to a group with EBV-DNA surveillance.
Method: From 3/2003 on in adult LT in Leiden EBV-DNA surveillance was used in the first year with lowering of immunosuppression in case of persistent positivity; the LTs from 3/2003 through 2018 formed the EBV monitoring group, and the LTs from 9/1992 till 3/2003 formed the historic control group without EBV monitoring. A third group was a contemporary control group of LTs without EBV monitoring transplanted 2003–2018 in Rotterdam with immunosuppression similar to the Leiden EBV monitoring group. Data were retrieved from the local transplant databases and patient charts. Kaplan-Meier survival analysis with exact Poisson regression analysis was used, p < 0.05 was considered significant.
Results: In the historic non-EBV-monitoring group 8/117 (6.8%) recipients developed PTLD, in the EBV monitoring group none of 322 developed PTLD (p = 0.0004 with an estimated incidence rate ratio of 18.59). In the contemporary non-EBV-surveillance group 10/606 (1.7%) recipients developed PTLD (p = 0.0084 with an estimated incidence rate ratio of 8.37). PSC was a risk factor for PTLD in both the historic and contemporary control cohorts (p < 0.01). Treatment of PTLD was successful in 7/8 cases in the historic controls and in 5/10 cases in the contemporary controls without EBV surveillance.
Conclusion: PSC is a risk factor for PTLD in adult LT and EBV-DNA surveillance in the first year after first LT in adult recipients, with IS reduction in case of persistently detectable EBV-DNA, can prevent occurrence of PTLD. It thereby can prevent morbidity and mortality.

THU229

De novo metabolic syndrome after liver transplantation: a prospective, longitudinal study

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Background and Aims: *De novo* metabolic syndrome (MS) is an emerging complication after liver transplantation (LT). This longitudinal, prospective study aimed to assess the prevalence and incidence of MS post-LT and its components and potential risk factors.
Method: patients without MS undergoing LT between April 2013 and October 2017 were prospectively included. Metabolic variables were collected at LT and at 6, 12 and 24 months post-LT. MS was defined according to the modified NCEP-ATP III criteria. In a sub-group of patients, CT-scan images were analysed by calculating skeletal muscle index (SMI), visceral adipose tissue index (VATI) and subcutaneous adipose tissue index (SATI) as predictors of post-LT MS.
Results: 63 patients were included (76% male, mean age 53.6 ± 9.5 years). The most common indication to LT was alcoholic liver disease (ALD) (38%). The prevalence of MS was 46%, 43% and 49% at 6, 12, and 24 months after LT, respectively, while its incidence was 46%, 57% and 68%. Among MS components, the prevalence of type 2 diabetes (T2DM) significantly increased after LT (33% at 6, 12 and 24 months post-LT vs. 16% pre-LT, p = 0.003), as well as hypertension (HT) (38% vs. 13%, p < 0.001; 37% vs. 13%, p = 0.001; 30% vs. 13%, p = 0.013, at 6, 12 and 24 months vs. pre-LT, respectively) and hypertriglyceridemia (31 vs. 14%, p = 0.035; 38% vs. 14%, p = 0.006, at 6 and 12 months vs. pre-LT, respectively). The incidence rates of T2DM, HT and obesity at 6, 12 and 24 months were 32%, 36% and 41%, 38%, 46% and 49% and 14%, 25% and 29%, respectively. At multivariate analysis, ALD was an independent risk factor for MS (HR 2.65, CI 1.12–6.29, p = 0.03) and obesity (HR 13.91, CI 1.57–122.77, p = 0.02), while high BMI pre-LT was predictive for HT (HR 1.11, CI 1.03–1.20, p = 0.007) and obesity (HR 1.82, CI 1.24–2.66, p = 0.002). Pre-LT impaired fasting glucose resulted predictive of T2DM (HR 1.02, CI 1.01–1.03, p = 0.001), conversely, the use of MMF was protective for T2DM (HR 0.18, CI 0.04–0.87, p = 0.03). In the sub-group undergoing body composition analysis (36 patients) sarcopenia was found in 23/36. High VATI was independently associated to the development of MS (HR 1.02, CI 1.00–1.04, p = 0.02) and HT (HR 1.02, CI 1.01–1.04, p = 0.01) after LT.
Conclusion: *de novo* MS is a frequent complication after LT showing a progressive increase overtime. A strict metabolic follow-up is mandatory starting early after LT, with particular attention for patients with established risk factors.

THU230
Phase angle is a prognostic nutritional marker in patients on the waiting list and after liver transplantation

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Background and Aims: Liver transplantation (LT) is the only curative treatment for end stage liver disease. Recently pre-LT assessment of nutritional status and functionality has gained attention given its prognostic implications; mainly CT scan and liver frailty index (LFI) have been used and validated, however, given the need for specialized software for CT scan and radiation exposure, and the lack of aplicability of LFI in patients with hepatic encephalopathy and bed-bound patients, more bedside and aplicable markers are available. Phase angle (PhA), a nutritional marker derived from bioelectrical impedance, is a portable, non-invasive, inexpensive method that can be performed in outpatients and hospitalized patients, as well as in those with hepatic encephalopathy, that could be useful in this population. The aim was to evaluate the association between PhA and the development of pre- and post-LTcomplications, and thus obtain a specific cut-off value for this population.
Method: Retrospective cohort study conducted at a tertiary care center (INCMNSZ) in Mexico City Patients with liver cirrhosis, of any etiology, that had PhA measurement were included. Patients with pacemakers, limb amputation and patients whose PhA measurement had been performed after LT were excluded. For the statistical analysis the Kolmogorov-Smirnov tests, descriptive statistics, ROC with Youden curves, Kaplan-Meier curves and Cox regression were used. SPSS v19 and MedCalc Version 19.0.5 were used. The study was approved by the Institutional Ethics Committee.
Results: 141 patients were included, 55% women, with an average age of 53 ± 13 years, AF of 4.5 ± 2.1, MELD of 17 ± 7 and the majority in Child-Pugh C stage (45.4%). The median follow-up was 224 (83–301) days, where at least one hospitalization was observed in 49.1%, the waiting list mortality was 35.7%; being the main cause septic shock (36.3%). 20.6% underwent LT, observing a post-LT mortality of 13.8% and 65.5% presented some complication, mainly of infectious origin (25%). According to the ROC curves, an AF <3.8 ° was associated with hospitalizations, and infectious complications before and after LT with AUC of 0.703, 0.683 and 0.704 respectively (p = <0.001). The Kaplan-Meier curves showed a greater survival in those patients with AF>3.8 ° vs with AF <3.8 ° 322 ± 17 vs 223 ± 24 days (p = 0.001). And finally, two multivariate models were created (to avoid collinearity) where the phase angle showed a higher risk of mortality HR = 1.98 (1.02–3.84) regardless of the severity of the disease according to MELD score and equally higher risk HR = 2.01 (1.02–3.94) regardless of the Child-Pugh stage.
Conclusion: A value of PhA less than 3.8 ° is associated with pre- and post-liver transplantation complications, mainly infectious, as well as hospitalizations and higher mortality, so this marker could be used in clinical practice as part of the pre LT nutritional assessment.

THU231
Differences of bile microbiology and antibiotic susceptibilities in liver transplant recipients from a non-transplant population with acute biliary infection

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Background and Aims: Because of immunosuppression, signs and symptoms of biliary infection in liver transplantation (LT) recipients are frequently subtler than those of non-transplant population that infection progresses easily to bacteremia, therefore the usage of effective antibiotics is important. However, there has been little study of bile microbiology and antibiotic susceptibilities in LT recipients with acute biliary infection that antibiotics recommended for non-transplant population is mostly administered to LT recipients in current situation and it sometimes do not effectively control the infection. Therefore, it is helpful to have an information of commonly isolated microorganisms and its antibiotic susceptibilities, especially in LT recipients with acute biliary infection to improve their clinical outcome that we investigated its differences between LT recipients and non-transplant population.
Method: We performed a comparative analysis of 376 positive bile cultures between LT recipients with biliary complication (n = 127, LT group) and non-LT population who underwent cholecystectomy for acute cholecystitis (n = 249, non-LT group) from January 2009 to December 2018 at multiple centers.
Results: There were significant differences of incidences of commonly isolated microorganisms between LT and non-LT group (P < 0.001); *Enterococcus* (31.5% vs. 26.5%), *Klebsiella* (18.1% vs. 12.4%), *Pseudomonas* (14.2% vs. 4.0%), *Escherichia* (11.0% vs. 29.3%), and *Enterobacter (*3.9% vs. 8.4%). Extended-spectrum beta-lactamase (ESBL) producing Gram-negative bacteria was significantly more common in LT group than non-LT group (62.9% vs. 13.0%, P < 0.001). Frequently isolated microorganisms were significantly changed over time after LT; *Enterococcus* (35.8%), *Klebsiella* (26.4%), and *Pseudomonas* (13.2%) within 6 months of LT and *Enterococcus* (28.4%), *Escherichia* (17.6%), and *Pseudomonas* (14.2%) after 6 months of LT (P = 0.029). Many of the commonly used antibiotics with a good effectiveness in non-LT group provided inadequate

coverage for frequently encountered microorganisms in LT group, except amikacin and imipenem against commonly isolated Gram-negative microorganisms and linezolid, streptomycin, and teicoplanin against *Enterococcus* including vancomycin-resistant *Enterococcus* sp. (VRE).
Conclusion: Differences of bile microbiology and antibiotic susceptibilities in LT recipients should be considered before selection of antibiotics in acute biliary infection.

THU233
Safety of marginal grafts in liver transplantation:a single-center experience
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Background and Aims: With the shortage of donors, the use of marginal donors has become more common in liver transplantation (LT). We aimed to assess the outcomes and experiences of LT from these marginal donors in a single centre study.
Method: We retrospectively analyzed all the database of LTs performed at our institution from January 2015 to October 2018. According to 2015 EASL clinical practice guidelines, the marginal grafts are defined as livers from donors >60 years of age, livers from donors with serum sodium levels >155 mEq, graft steatosis >30%, livers with cold ischemia time ≥ 12 hours, livers from donors who were hepatitis B or C virus positive, livers recovered from donation after cardiac death, and livers split between 2 recipients. Patients receiving marginal grafts (marginal group) were compared with patients receiving standard grafts (standard group).
Results: There were 356 patients in the standard group and 237 patients in the marginal group. No significant differences were found in terms of age, sex, Model for End-Stage Liver Disease score, underlying liver disease, presence of hepatocellular carcinoma, and hospital stay between the 2 groups. The incidence of acute cellular rejection, cytomegalovirus infection, and postoperative complications was similar between the 2 groups. But the incidence of early allograft dysfunction was higher in the marginal group. Patient overall survival and graft survival (death-censored) were significantly lower in the marginal group ($P < 0.05$). On multivariate analysis, receiving a marginal graft was significantly associated with worse patient overall survival($P < 0.01$). Also, when factors associated with marginal graft were analyzed separately, graft steatosis >30% and cold ischemia time ≥ 12 hours were independently associated with survival ($P < 0.05$).
Conclusion: Marginal grafts could be a acceptable way for LT because of shortage of donors, but the standard limit should be under critical assessment, such as graft steatosis >30% and cold ischemia time ≥ 12 hours may not suitable for LT.

THU234
Severe obesity increases death and dropout from liver waiting list: French liver transplant cohort
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Background and Aims: As obesity is increasing, new challenges are emerging in the management of severe obese (BMI>35 kg/m²) on the liver transplant waiting list. Indeed, severe obesity is related to increased morbidity after transplant and a reduced access to liver transplantation (LT) in the US. We studied the outcomes of severe obese patients on the French liver waiting list (WL) and the reason of graft refusal.
Method: Analyses were performed in adult candidates listed between January 2007 and December 2017 (MELD era). Data were extracted from the prospective national database of the French Transplant Agency. The study was conducted in two steps. First, competing risk analyses were performed to evaluate predictors of receiving a LT. The outcomes of death/waitlist removal due to disease aggravation and waitlist dropout owing to improvement were considered as competing events. Patients still on the WL or dropped-out due to personal decision were censored. Second, we evaluated the potential link between severe obesity and graft propositions, and then the causes of graft refusal.
Results: 15 184 registrations occurred between 2007 and 2017. At time of analysis, 10 813 patients were transplanted, 2 847 were dead or dropout from the list for disease aggravation, 748 were redirected for disease improvement and 776 censored.
Characteristics of patients were: age 56 ± 10.4, male gender 74.2%, BMI 26.2 ± 5.3 kg/m² (6.3% of severe obesity), MELD 15.8 ± 10.7. Severe obese patients were older (55.8 ± 8.5 vs. 54.2 ± 10.5) more diabetic (36.9 vs. 22.2%), higher MELD (16.6 ± 11.3 vs. 15.7 ± 10.7) and were frequently registered for HCC (39.2 vs 32.4%).
After adjustment in multivariate analysis, severe obesity, higher age, hepatic encephalopathy and ascites were independent predictors of death and drop out due to disease aggravation. In addition, severe obesity was reducing access to LT.
At least one graft has been proposed to the included patients in 82.6% of cases. Before LT or waiting list dropout, 4.4 ± 7.7 grafts were proposed per patients. There was no difference in terms of number of propositions between severe obese and non-severe obese patients. However in severe obesity, grafts were more frequently refused especially for "morphological incompatibility."
Conclusion: Severe obese patients are disadvantaged on the WL with lower access to LT and higher drop out of the WL. Indeed, in this subgroup graft refusal is more frequent, in particular for morphological reasons.

THU236
Liver transplantation assessment: what are the factors associated with contraindication for listing or delayed activation on waiting list?
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Background and Aims: LT assessment is a challenge for patients with Alcohol-Related Liver Disease (ALD) and Nonalcoholic Fatty Liver Disease (NAFLD) with multiple comorbidities (metabolic syndrome and cardiovascular disease (CVD)). The aim of this study was to evaluate the factors associated with a contraindication for LT listing and delayed activation on waiting list.
Method: From 2014 to 2019, all patients (n = 895) with an indication for LT were retrospectively screened for inclusion. A total of 588 (65.7%) cirrhotic patients were assessed for LT: 143(24.3%) patients were contraindicated, and 445(75.7%) patients were listed for LT. On the list, 275(61.8%) were activated with no delay and 170(38.2%) with delay (Figure).
Results: The main causes of contraindication were CVD (n = 36;25.2%), active alcohol consumption (n = 34;23.8%) and advanced hepatocellular carcinoma (HCC) (n = 29;20.3%). In univariate analysis, the factors significantly associated with contraindication for LT listing were: age>60 years (53.8%*vs.*39.3%, p = 0.002), ALD (74.1%*vs.*64.7%, p

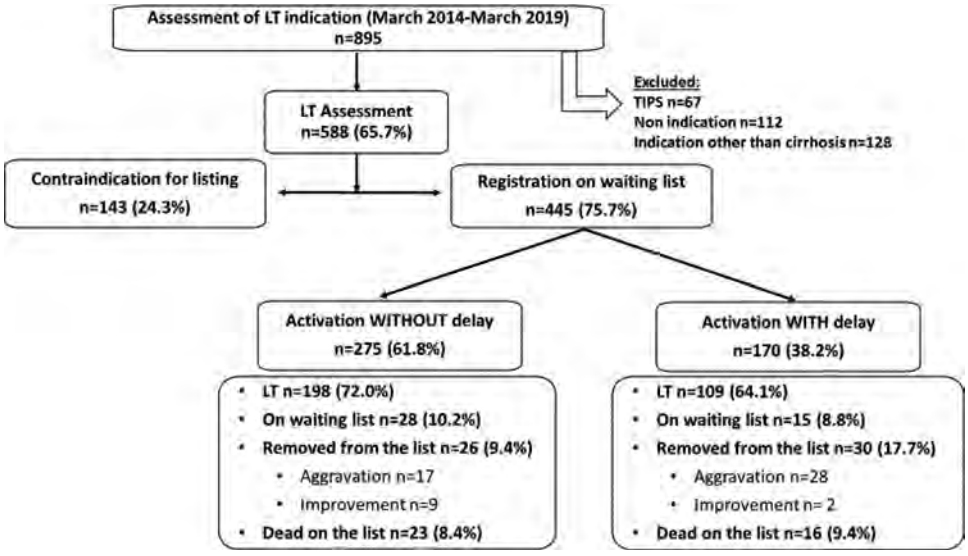

Figure: (abstract: THU236): Flow Chart of the study.

= 0.04), hypertension (49.7% *vs.*38.4%, p = 0.02), dyslipidemia (21.7% *vs.*13.5%, p = 0.02), MELD score ≥ 30 (20.3% *vs.*8.8%, p = <0.0001). Factors not associated with LT contraindication were metabolic syndrome, BMI>30 kg/m^2, male sex, NAFLD and active smoking. In multivariate analysis, age>60 years old (OR = 1.9; IC95:1.27–2.79), ALD (OR = 1.6; IC95:1.02–2.42) and MELD score ≥ 30 (OR = 3.0; IC95:1.75–5.15) were significantly associated with LT contraindication. The main causes of delayed activation on the list were the need for specific investigations (38.8%), infection (27.6%), and interventions (coronary stenting)(24.1%). In univariate analysis, factors significantly associated with delayed activation on the list were: hepatitis C (21.8%*vs.*12.4%, p = 0.009), metabolic syndrome (25.9% *vs.*17.5%, p = 0.033), registration for MELD exception (24.7%*vs.*13.5%) or HCC (46.5%*vs.*40.4%) (*vs.* MELD score (28.8%*vs.*46.2%)) (p < 0.0001), and antiplatelet therapy (25.3%*vs.*5.8%, p < 0.0001). In multivariate analysis, factors associated with delayed activation on waiting list were: hepatitis C (OR = 2.4; IC95:1.4–4.3), antiplatelet therapy (OR = 6.9; IC95:3.6–13.7), MELD score<30 (OR = 6.7; IC95:2.1–21.5), registration for MELD exception (OR = 2.2; IC95:1.2–3.8) or HCC (OR = 2.2; IC95:1.2–3.9).

Conclusion: Assessment before LT leads to contraindication or delayed activation on waiting list in a large proportion of cirrhotic patients, because of associated co-morbidities and complications of cirrhosis.

THU237

Anticoagulation in liver transplant candidates: a case control study

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Background and Aims: In liver transplant candidates, indication for anticoagulation are diverse, including portal vein thrombosis (PVT), and anticoagulation can be associated with bleeding complications. The aim of this study was to evaluate the safety of anticoagulation in a large series of liver transplant candidates.

Method: In two tertiary care centers, all patients listed for liver transplantation (LT) from January 2010 to March 2018 were screened for anticoagulation treatment. All patients treated with anticoagulation were compared to liver transplant candidates with no anticoagulation. The two groups were matched on: age, year of registration, MELD score, cause of cirrhosis and gender. Patients' clinical characteristics, indication for anticoagulation, bleeding events, hospitalisation, transfusion requirements and surgical complications during LT were collected.

Results: Of the 852 patients listed for LT, 70 (8.2%) were treated with an anticoagulant (PVT n = 61 (87.1%)). Bleeding events occurred in 28 patients (40.0%) treated with anticoagulation and in 11 patients (15.7%) in the control group, mostly related to portal hypertension in both groups (Figure 1). The median time from the beginning of anticoagulation to bleeding event was 2.7 months (IQR: 0.9–7.7) Ten patients (35.7%) patients had a definitive withdrawal of anticoagulation. In univariate analysis the factors associated with bleeding events were: anticoagulation (p = 0.01), PVT (p = 0.04), MELD score ≥ 18 (p = 0.03) and decompensated cirrhosis (p = 0.06). In the anticoagulation group, in univariate analysis, male sex was the only factor associated significantly with a higher risk of bleeding events (p = 0.03) while the type of anticoagulant (VKA or LMWH) (p = 0.34), the extension of PVT (p = 0.67) and platelets count <70 Giga/L (p = 0.65) were not associated with a significant risk of bleeding. In multivariate analysis, anticoagulation was the only factor significantly associated with bleeding events (HR = 3.5; IC95: 1.7–6.9; p < 0.001). Anticoagulation was not associated with a higher wait list mortality (p = 0.14). At LT, 37 patients had PVT and 92.8% had end to end portal anastomosis. Blood loss was significantly more important in the anticoagulation group (p = 0.03) but there was no difference in blood transfusions (p = 0.14).

Conclusion: In liver transplant candidates, anticoagulation is associated with a high risk of bleeding events on waiting list mainly related to portal hypertension.

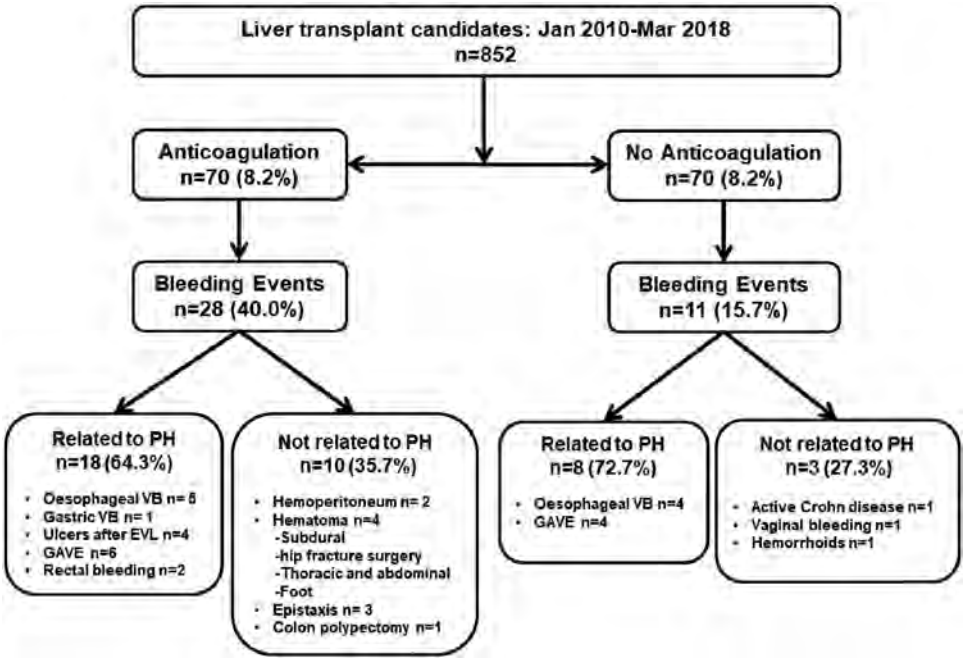

Figure: (abstract: THU237): Flow Chart of the study; *Abbreviations*: PH: Portal Hypertension; GAVE: Gastric antral vascular ectasia; VB: variceal bleeding.

THU238

Pre-transplant sarcopenic obesity worsens the survival after liver transplantation: a meta-analysis and systematic review

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Background and Aims: Sarcopenic obesity (SO) - loss of skeletal muscle mass with an increased fat mass - is a common complication of end-stage liver disease and is considered among the predictive factors for increased morbidity and mortality in several diseases. Our aim was to evaluate the effect of pre-transplant SO on the outcomes of liver transplantation (LT).
Method: A comprehensive search was performed on 27th March 2019 in seven medical databases for studies which discussed patients subjected to LT and compared the effect of pre-transplant radiologically-proven SO to that of non-SO. The primary outcome was overall mortality at short- (1–2 years), intermediate- (2–5 years), and long-term (>5-years). In the meta-analysis, pooled relative risks (RRs) with 95% confidence intervals (CIs) were calculated. Heterogeneity was quantified with I2-statistics.
Results: Altogether, 4 articles were eligible for inclusion. Based on the analysis of 1515 patients, SO increased overall mortality compared to non-SO at short-, intermediate-, and long-term (RR = 2.06, 95% CI: 1.28–3.33; RR = 1.67, 95% CI: 1.10–2.51; and RR = 2.08, 95% CI: 1.10–3.93, respectively), without significant between-study heterogeneity. The amount of data did not allow us to compare SO to normal or other pathological body compositions.
Conclusion: Pre-transplant radiologically-proven SO proved to be a risk factor of mortality after LT. Further research is called for to investigate the effect of SO in relation to other body compositions and by underlying etiology of liver diseases.

THU239

Women benefit more from having a potential living liver donor than men

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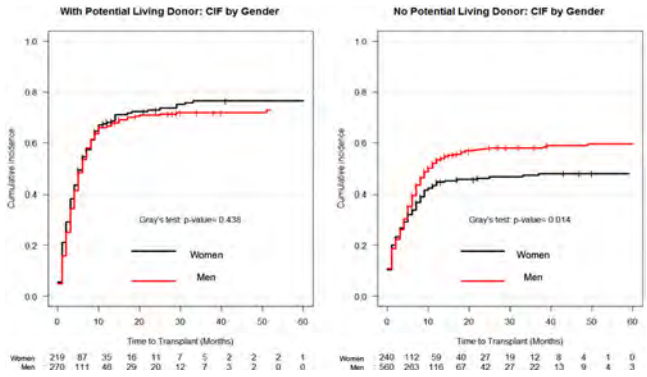
Background and Aims: It is well recognized that there is a disparity in liver transplantation (LT) rates between men and women. Several factors account for this disparity, including smaller body size and lower muscle mass leading to lower serum creatinine in women. We sought to determine whether the presence of a Potential Living Donor (PLD) helps women gain better access to LT.
Method: We performed a retrospective analysis of data on adult patients above the age of 18 listed for LT from November 2012 till December 31, 2018. Patients were followed till the time of dropout from the waiting list and LT. Subgroup analysis was done based on gender and type of LT. Patients with acute liver failure and those requiring exception points for listing were excluded. Variables that would potentially influence listing and LT were identified based on a-priori clinical relevance. A PLD referred to an individual who had stepped forward for living donation and had completed the initial assessment as well as imaging assessment.
Results: 783 of 1289 listed patients (573 deceased donor LT, 210 living donor LT) underwent LT during the study period. In the group with no PLD at assessment: a) 46.13% failed to attract LT and NaMELD score did not differ between men and women at the time of listing or drop out, b) in patients eventually receiving deceased donor LT, women had both a higher NaMELD at listing ($p = 0.0004$) and at LT ($p < 0.0001$) compared to men. In the group with PLD, NaMELD score did not differ between gender at time of listing, LT or drop-out. Fine and Gray model suggested that in the no PLD group, the cumulative incidence curve for time to LT was higher in men than women ($p = 0.014$) (Figure 1), whereas there was no gender difference detected in the PLD group ($p = 0.44$). Cox PH model revealed a trend of higher overall survival in

men than in women (p = 0.08) in the no PLD group and no difference was found in the PLD group (p = 0.93). Also, among women with no PLD, taller women were associated with higher chances of LT (HR 1.04, 95%CI 1.01–1.07, p = 0.01).



Conclusion: With no PLD during assessment, women were at potential risk of lower survival and were significantly disadvantaged at receiving LT compared to men. Women receiving LT were much sicker than their male counterparts both at time of listing and at time of LT, and were taller than other women who failed to receive LT. When PLD were identified at time of assessment, access to LT and overall survival improved for women and their results became comparable with men.

THU240

Transmission and impact of donor allergies in living donor liver transplantation

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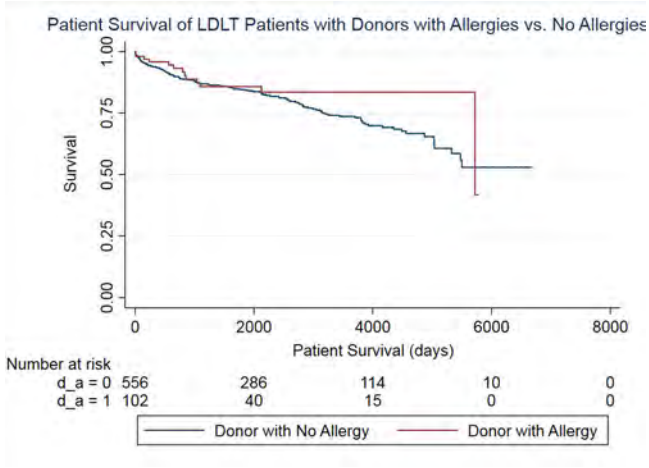
Background and Aims: The transmission of donor allergies at time of liver transplant (LT) has been clearly documented in the literature. However, there is lack of large studies or case series regarding the frequency of transfer of drug allergies, in addition to clear data regarding the impact, if any, on rejection or graft and patient outcomes.
The aim of this study was to identify the number of living liver donors with allergies, to estimate the risk of post-transplant transmission of donor allergies and to assess if the presence of donor allergies had an impact on incidence of rejection or graft and patient survival after living donor liver transplantation (LDLT).
Method: This was a retrospective, single-centre analysis of adult patients who received a LDLT from 2000–2018. Donor allergies were classified according to World Allergy Organization Systemic Allergic Reaction Grading System. Transmission of allergies was assessed by individual chart review. The incidence of post LT rejection and patient/graft survival outcomes (graft from an allergic donor versus non-allergic donor) were compared.
Results: 667 recipients had a LDLT during study period (418 had LDLT from related donor). 103 donors had documented >/ = grade 3 allergy (79 donors had grade 3 allergy and 24 had grade 4/5 (history of anaphylaxis)). All recipients were followed in our program and there was no documented transfer of allergies from the donor to recipient. There was no significant difference in the rejection rates and overall survival in the LDLT group receiving liver from donors 24 with severe allergies.



Conclusion: The presence of a donor allergy does not adversely affect the outcome of the recipient of a LDLT

THU241

Postreperfusion biopsy as predictor of outcomes after liver transplantation

Esteban Fuentes Valenzuela[1], Rodrigo Najera[1], Javier Tejedor Tejada[1], Carlos Maroto Martín[1], Laura Sanchez Delgado[1], Beatriz Madrigal Rubiales[2], Carmen Alonso Martin[1], Fátima Sánchez Martín[1], Félix García Pajares[1], Carolina Almohalla Alvarez[1], Gloria Sánchez Antolin[1]. [1]*Hospital Universitario Rio Hortega, Hepatology and Liver Transplantation Unit., Valladolid, Spain;* [2]*Hospital Universitario Rio Hortega, Department of Pathology, Valladolid, Spain*
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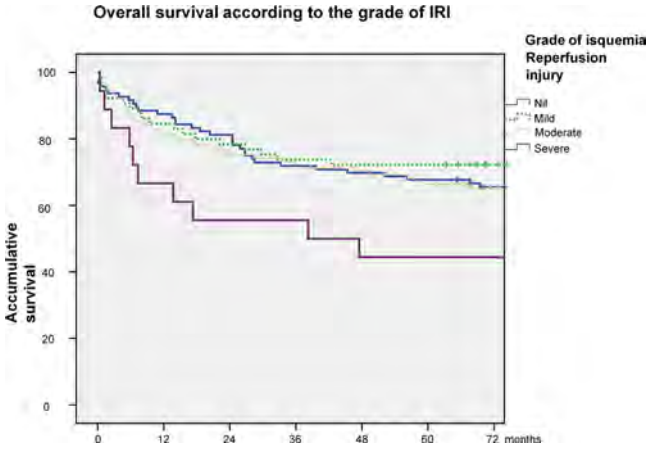
Background and Aims: Postreperfusion liver biopsy (PRB) assess the degree of ischemia reperfusion injury (IRI) after liver transplantation (LT). There are few studies about Its influence on the graft outcomes and overall survival. The aim of our study was to know the correlation between the severity of IRI in the PRB, the overall graft and patient survival and the predictor factors.
Method: We performed a retrospective study in all LT patients with a PRB, between January 2001 and June 2014 in our center. The independent predictor factors and the survival analysis were determined with Cox regression and Kaplan Meier, respectively. The early primary graft dysfunction (EPGD) was defined by the presence of one or more of the following: total bilirubin >10 mg/dl, INR >1,6 or ALT > 2000 U/l within the first week after LT. The initial poor graft function (IPGF) was determined as AST > 1,500 U/l or ALT > 1,000 U/l. The primary nonfunction (PNF) was defined as the need for urgent transplant or death. The severity of IRI on the PRB was graded as nil, mild, moderate, and severe.
Results: Out of 433 LT performed during this period, 280 patients with PRB were included in our study (64.9%), 77.5% were males. The main LT indication was decompensated cirrhosis 47.9%. The median MELD score was 13.0 (IQR 10–17). The donors' average age was 57.9 (SD+/–17.5). The cold ischemia average time was 402.3 (SD +/–91.9). The PRB were graded as follows: nil (34.3%), mild (23.2%), moderate (66.3%), and severe (5.4%). The incidence of IPGF, PNF and EPGD was 32.5%, 3.9%, and 18.6%, respectively. The severe IRI was associated with higher incidence of IPGF (p = 0.04), but no statistically significant differences were found in the incidence of PNF (p = 0.52) and EPGD (p = 0.27). Although patients with severe IRI tended towards higher incidence of EPGD (33.2% vs 18.6). Only the cold ischemic time was an independent predictor factor of severe IRI HR 1.006 (95% CI 1.001–1.011). The severe IRI was associated with poor 1 and 5-year overall survival rates (67% and 44%, compared with 84 and 68%). Patients with severe IRI had worse overall survival, although not

statistic significant (Figure 1) (p = 0.06). Patients who developed EPGD had worse overall survival (p = 0.002).



Conclusion: Cold ischemia time predicts the development of severe IRI. Patients with severe IRI tended towards a worse overall survival and higher incidence of EPGD. Moreover, the development of EPGD itself could be predictor of overall survival.

THU242

Sarcopenia HIBA score predicts the presence of sarcopenia and mortality in patients on the waiting list for liver transplant

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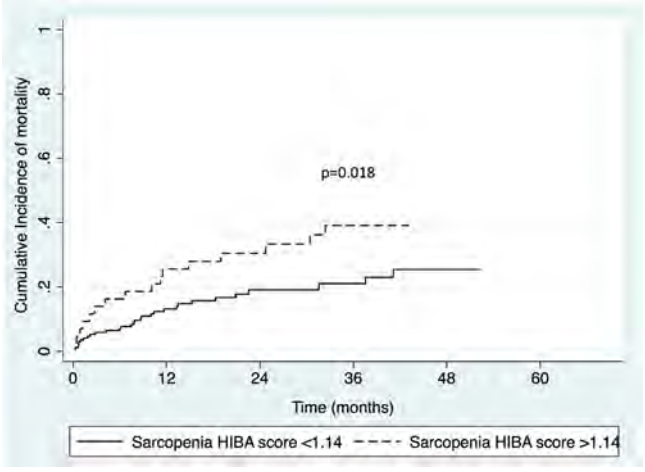
Background and Aims: Sarcopenia is a prevalent condition that predicts an unfavourable prognosis in patients with cirrhosis included on the waiting list (WL) for liver transplant (LT). The gold standard for the diagnosis of sarcopenia is based on the assessment of the muscular area at L3 with CT scan (Skeletal Muscle Index, SMI). Since the routine use of CT scan is limited in clinical practice due to cost and exposure to radiation, Sarcopenia HIBA Score has recently been postulated as an indirect score to predict the presence of sarcopenia by SMI. Our aim was to evaluate the capability of Sarcopenia HIBA Score to predict mortality in patients on the WL
Method: Monocentric retrospective study in which a cohort of patients with cirrhosis was included in the WL for LT (January 2014 to April 2019). The sarcopenia HIBA score was defined by the following formula: Male * 2.344 + BMI*(−0.372) + Alkaline Phosphatase * (−0.005) + Child Pugh * (0.308) + Creatinine/Cystatin-C * (−4.547) + 9.057. All the variables, including the presence of sarcopenia by skeletal muscle index and sarcopenia HIBA score were collected at the time of the inclusion on the WL. The predictive factors of mortality in the WL were evaluated with competing risk regression analysis (with LT as the competing risk of mortality in WL). We described the 80-percentile threshold of Sarcopenia HIBA score to rule in sarcopenia (>1.14) for the analysis of cumulative incidence of mortality.
Results: A total of 215 patients with cirrhosis listed for LT were included: 38% female, median age 59 years, main etiologies were liver disease alcohol, HCV and NASH. The main indication of LT was decompensated cirrhosis (85%). The prevalence of sarcopenia by SMI was 43%. The median follow-up was 11.7 (4.9–25.8) months. During the follow-up 77 (36%) patients underwent LT, 46 (21%) died and 92 (43%) remained alive. After adjusting for MELD-Na, Sarcopenia HIBA score was an independent predictor of mortality in the WL (sHR1.19; 95% CI 1.01–1.40; p = 0.042).



Conclusion: Higher values of Sarcopenia HIBA score are independently associated with mortality in WL. The assessment of this risk factor may improve the prognostic evaluation and allow identifying a group of patients with a risk of death while awaiting LT.

THU243

A novel nomogram based on liver stiffness to predict the comprehensive complication index after liver resection in patients with hepatocellular carcinoma

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Background and Aims: Liver stiffness measurement (LSM) assessed by transient elastography (FibroScan®) has been demonstrated to predict post-hepatectomy liver failure (PHLF) in patients undergoing hepatic resection for hepatocellular carcinoma (HCC). However, other complications, besides PHLF, can be related to the underlying grade of liver fibrosis. This study aimed to identify predictors of postoperative complications calculated by the comprehensive complication index (CCI) and to build and develop a novel nomogram able to identify patients at risk of developing severe postoperative complications.
Method: Data of patients treated by hepatectomy for HCC between 2006 and 2016 at two referral centres, were retrospectively reviewed. All surgical complications were recorded and scored using the CCI, ranging from 0 (uneventful course) to 100 (death). A CCI ≥26.2 was used as a threshold to define patients having severe complications.
Results: During the study period, 471 patients underwent hepatic resection for HCC. Among them, 50 patients (10.6%) had a CCI ≥ 26.2. Age, MELD score and LSM values together with serum albumin were independent predictors of high CCI. The nomogram built on these variables was internally validated and showed good performance (C-statistic = 0.797). A regression equation to predict the CCI was also established by multiple linear regression analysis: [LSM (kPa) × 0.254] + [age(years) × 0.118] + [MELD score(pt.) × 1.050] – [albumin (g/dL) × 2.395] – 3.639.
Conclusion: This novel nomogram, combining LSM values, age and liver function tests provided an excellent preoperative prediction of high CCI in patients with resectable HCC. This predictive model could be used as a reference for clinicians and surgeons to help them in clinical decision-making.

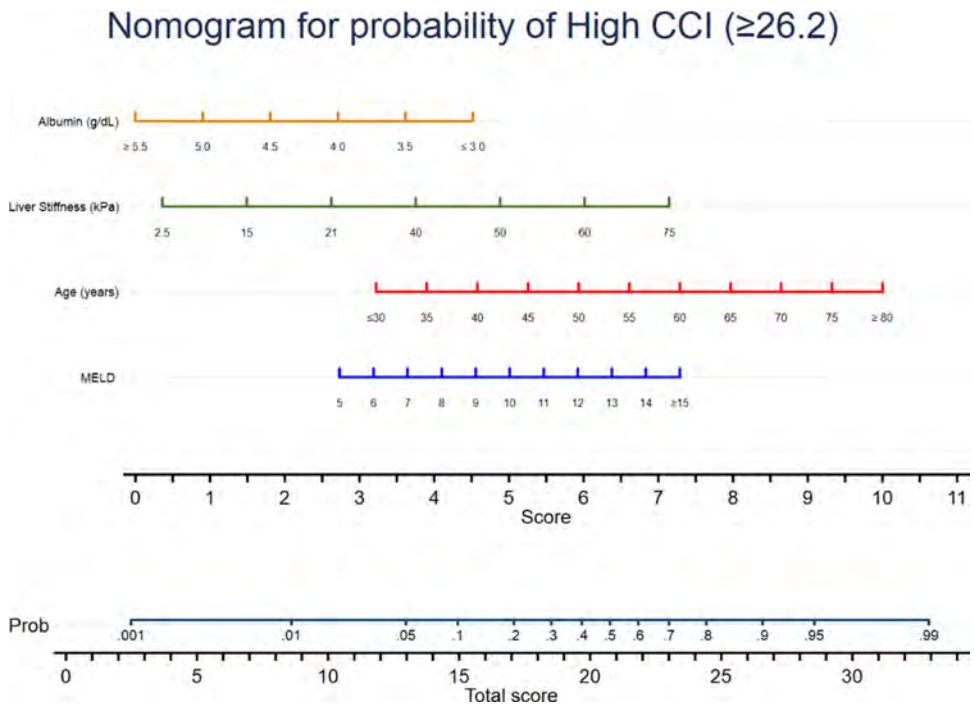

Figure: (abstract: THU243)

THU244

Physical frailty predicts liver transplant waiting list mortality: United Kingdom experience

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Background and Aims: Patients awaiting liver transplantation (LT) have reduced physiological reserve and increased vulnerability to health stressors – known as physical frailty (Lai et al., 2017). Physical frailty is associated with poorer clinical outcomes, however there remains paucity of data on physical frailty in European populations. We aimed to prospectively investigate the incidence and impact of physical frailty in patients awaiting LT in the United Kingdom (UK).
Method: From 2018–2019, patients were consecutively recruited from the LT assessment and waiting list clinics at the University Hospital Birmingham, UK. The Liver Frailty Index (LFI) (hand grip, chair stands, balance; https://liverfrailtyindex.ucsf.edu) and Duke Activity Status Index (DASI) (predicted VO_2 peak) were used to evaluate physical frailty. Clinicians were blinded to the results omitting any influence on organ allocation or LT waiting list status. Patients were prospectively followed up for a minimum of 4 months.
Results: 307 patients (57% male; median age 54 years; 46% ALD/NAFLD) were recruited. The median UKELD and MELD were 52 (IQR 49–55) and 13 (IQR 9–16), respectively. 37% (114/307) were obese (BMI > 30 kg/m^2) and 27% (82/307) had metabolic syndrome. During follow-up, 40% (123/307) underwent LT and 4.6% (14/307) died whilst waiting.

Median LFI was 3.76 (IQR 3.31–4.29), with 20% (60/307) classified as robust, 65% (201/307) pre-frail and 15% (46/307) frail. These parameters are similar to that reported in North America (Figure 1) (Lai et al., 2017). Median VO_2peak was 21.9 (IQR 16.6–31.2) ml/kg/min. LFI (alive 3.77 vs. death 4.22; $p = 0.017$) and VO_2peak (22.6 vs. 16.4 ml/kg/min; $p < 0.001$) were significantly associated with waiting list mortality. Furthermore, both LFI and VO_2peak were associated with increased intensive care length of stay post-LT ($p = 0.03$).

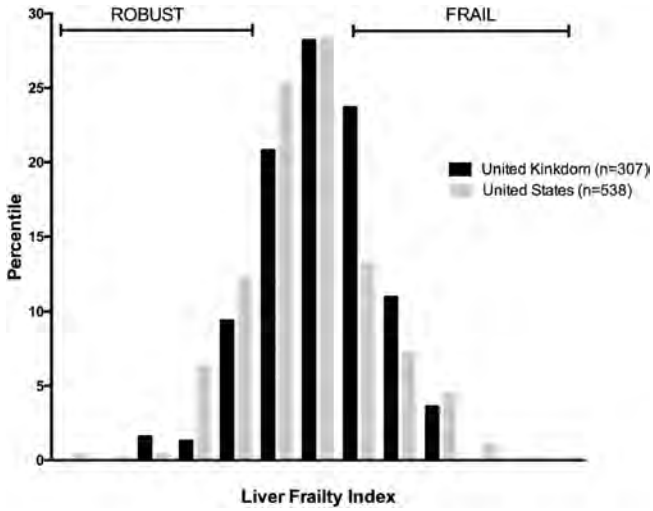

Figure: A comparison of Liver Frailty Index scores in the UK and US

Female sex, age, BMI, hyponatraemia, INR, encephalopathy and ≥ 2 metabolic co-morbidities were significantly ($p < 0.05$) associated with higher LFI (*physical frailty*). VO_2 peak significantly correlated with LFI ($r = -0.56$; $p < 0.001$). Older age ($p = 0.003$) and hyponatraemia ($p = 0.016$) were independent predictors of physical frailty (LFI) on multiple linear regression analysis.
Conclusion: A significant proportion of patients awaiting LT are physically frail. Risk factors include female sex, older age, obesity,

metabolic syndrome and encephalopathy. Markers of physical frailty, LFI and DASI, predict LT waiting list mortality.

THU245

Early versus late hepatocellular carcinoma (HCC) recurrence after liver transplantation for HCC: patterns and long-term outcome

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Background: Hepatocellular carcinoma (HCC) is the most common indication of liver transplantation (LT). HCC recurrence is the main complication affecting short and medium term outcome after liver transplantation (LT). The aim of this study is to analyze the patterns and outcome of patients who developed HCC recurrence according to post-transplant time of recurrence.
Method: Consecutive patients who underwent LT for HCC between 2000 and 2017 at our center were recruited. Characteristics of patients, recurrence, modalities of treatment and outcome were collected retrospectively. Patients were divided according to time of recurrence: early (≤2 years post-transplant) and late (>2 years post-transplant).
Results: 433 patients (mean age: 57.8 ± 8.5 years; 83.8% were males) underwent LT for HCC. Mean follow-up was 74.6 ± 58.6 months. Seventy-five patients (17%) developed HCC recurrence with a mean time to recurrence of 29.7 ± 31.8 months. Patient who developed recurrence had as expected more tumors outside Milan and UCSF criteria, a significantly high AFP score and microvascular invasion at pathology. Recurrence site at diagnosis was intrahepatic only (16.0%), extrahepatic only (61.3%) and intrahepatic and extrahepatic (22.7%). 71.2% of the recurrent HCC cases were treated by systemic chemotherapy. The mean AFP level at the time of diagnosis of early HCC recurrence 1061 ± 3545 ng/mL and 292 ± 805 ng/mL in the late HCC recurrence group. Early recurrence developed in 46 patients (61.3%) and late recurrence occurred in 29 patients (38.7%). The median survival times from the diagnosis of the HCC recurrence were similar 15 months and 17 months respectively in the early and late recurrence groups (p = 0.12). The 5,10 and 15-year patient survival of the whole cohort were respectively 74.6%, 59.0% and 48.6%. The overall 5, 10 and 15-year recurrence free survival rate was 70.6%, 55.4% and 46.3%. Among the patients who developed an early HCC recurrence the overall 5, 10 and 15-year survival rates were similar 6.7% and significantly shorter than those patients with late recurrence respectively at 5,10 and 15 years, 64.0%, 27.1% and 0% (log rank p < 0.0001).
Conclusion: In this large cohort with long-term follow-up, late HCC recurrence has been associated with a good long-term survival. Early HCC recurrence is associated with very bad prognosis, in relation to more aggressive tumor and either tumor progression or bad selection criteria at time of transplant.

THU246

Epidemiology, features and outcome of patients transplanted for hepatocellular carcinoma in the last decade: a single-center experience

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Background and Aims: Hepatocellular carcinoma (HCC) represents an increasing indication for liver transplantation (LT) world-wide but the burden and clinical implications of post-transplant HCC recurrence is still debated. Aim of this study was to identify recurrence rate, survival and predictors of recurrence in HCC patients consecutively transplanted in the last 10-years.
Method: retrospective, single center study including all consecutive LT patients with HCC from 01/2010 to 07/2019. HCC-recurrence surveillance was performed with CT-scan and AFP every 6 months for the first 5-yrs after LT. Immunosuppression was CNI-based.
Results: 182 HCC out of 449 transplanted patients (41%) were studied: 84% males, median age 58-yrs, 60% HCV, 25% MELD ≥ 15, median AFP at LT 9 ng/ml; median time-lag between HCC diagnosis and LT was 17 months, pre-LT bridging/down-staging therapy in 74%. At explant pathology: 16% showed micro-satellitosis, 27% micro-vascular invasion (mVI), 50% Edmonson score = G3/4; 76% were "Milan"-in, 11% were "Milan"-in and "Up to 7"-in while 13% "Up to 7"-out. During a median follow-up of 42 months, HCC recurred in 29 patients (16%) after a median time of 9 (2–46) months. Probability of recurrence at 1-, 3-, 5-yrs was 5%, 11% and 15%, respectively. By multivariate analysis, independent risk-factors for HCC recurrence were micro-satellitosis (HR = 0.31, p = 0.023) and microvascular invasion (HR = 0.38, p = 0.04). Overall probability of survival at 1-, 3- and 5-yrs was 94%, 87% and 77%, respectively; being 95%, 89% and 85% in the recurrence-free patients vs 89%, 76% and 43% in the recurrence-group (p < 0.005). Those patients who were transplanted after 2015 (n = 108), significantly differed from those transplanted before 2015 (n = 74), since they were older (p = 0.04), more frequently males (p = 0.02), with lower MELD (p = 0.0001) at transplant, more frequently treated by locoregional therapies for bridging/down-staging purposes (p = 0.002) and with higher rates of G3/4-HCC (p = 0.001) at explant pathology, however with similar post-transplant overall survival [100.9 (95%CI 90.16–111.8) vs 91.4 81.7–101.1) months (p = 0,15)].
Conclusion: Our study confirms tumor-related features at explant pathology as predictors of HCC recurrence. Moreover, in the last few years we have transplanted older patients with less severe disease but with more advanced tumors, while maintaining survival figures well fitted with a transplant benefit.

THU247

Early recurrence of hepatocellular carcinoma after liver transplantation can be predicted by FDG-PET and microvascular invasion at explant pathology

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Background and Aims: Hepatocellular carcinoma (HCC) may recur early after liver transplantation (LT), because of pre-transplant dissemination of primary tumor cells, mainly through blood vessels. One of the main driver for recurrence is microvascular invasion, which is not always detectable by pre-operative imaging examination, as CT-scan and contrast enhanced-MRI, however the role of F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) is poorly investigated in this setting. Our study aimed to identify predictors of the recurrence of HCC after LT, including FDG-PET, with particular attention to early recurrence (≤12 months) risk.
Method: This is a single center, retrospective study including all consecutive patients who underwent LT for HCC as the main indication since 01/2010. Epidemiological, clinical, radiological and histological data were collected and analysed.
Results: Between 01/2010 and 07/2019 449 patients have been transplanted in our center, 182 (41%) with HCC: 158 (84%) males, median age 58 (36–71) years, 60% HCV-Ab positive, 25% MELD-score ≥15, 54% Child-Pugh stage A, median AFP at LT 9 (1–60,500) ng/mL, 29% resulted FDG-PET positive. The histopathological evaluation of the native liver revealed: 86% explanted liver with at least one active HCC nodule [median number per liver 2 (1–22)] with a median size of 32 (3–239) mm; 16% with micro-satellitosis and 27% with micro-vascular invasion (mVI). During a median follow-up of 42 (2–118) months, HCC recurred in 29 (16%) patients (Probability of recurrence at 1–3–5-yrs was 5–11–15%, respectively): 13 recurred within 12 months after LT (early recurrence group) and 16 >12 months. By univariate analysis, the risk-factors for early-recurrence were micro-satellitosis, mVI, G3/4, FDG-PET positive, Milan-out criteria, however only mVI and FDG-PET positivity were confirmed by multivariate analysis as independent predictors for early-recurrence (HR 0.22, p = 0.019 and HR 0.11, p = 0.09). The over-all survival in our cohort was 96 months (95%CI:20–89), being 49 months (95%CI:20–78) in the 13 early-recurrent patients, 64 (95%CI:39–89) in the 16 late-recurrent ones and 104 (95%CI:21–85) in non-recurrent ones.
Conclusion: The FDG-PET in the pre-LT setting and microvascular invasion at explant pathology may help to identify those patients at high risk of early HCC recurrence, deserving of aggressive surveillance or pre-emptive systemic treatment after LT.

THU248

Re-establishing abstinence after alcohol relapse after early transplant (LT) for alcoholic hepatitis (AH) provides survival advantage

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Background and Aims: Alcohol relapse after early LT for AH is the strongest predictor of post-LT death. To inform post-LT alcohol interventions, using the ACCELERATE-AH (American Consortium of Early Liver Transplantation for Alcoholic Hepatitis), we sought to identify factors associated with establishing abstinence in patients with harmful alcohol relapse after early LT for AH, and to determine whether re-establishing abstinence after alcohol relapse can abrogate the effects of alcohol relapse on survival.
Method: Detailed post-LT alcohol use data in 3-month intervals was retrospectively obtained from 11 ACCELERATE-AH sites. Consecutive patients with clinically-diagnosed severe AH and no prior diagnosis of liver disease who underwent LT from 2006–2018 were included. Latent class analysis and Cox regression identified longitudinal harmful patterns of alcohol relapse, defined as alcohol use patterns associated with increased risk of post-LT death. Patients with harmful relapse post-LT were classified as "established abstinence after relapse" vs. "continued use" as determined by the alcohol use during the last interval of follow-up. Logistic regression examined associations of pre-LT and post-LT variables with establishing abstinence after relapse, adjusted for center clustering.
Results: A total of 146 AH patients underwent LT [67% male, median pre-LT abstinence 59 days) with a median of 3.0 years (IQR 2.0–4.6) post-LT follow-up: 18% for ≥5 years. Median post-LT hospital stay was 14 days (IQR 9–24). 34 patients had harmful relapse: 22 had

continued use after relapse, whereas 12 re-established abstinence after relapse. There were 17 post-LT deaths, of which 10 were alcohol-related. 11 post-LT deaths occurred in patients with continued use after relapse, whereas only 1 post-LT death occurred in patients who re-established abstinence after relapse (p = 0.008). In multivariable analysis, compared to abstinence/non-harmful use, establishing abstinence after relapse was associated with similar risk of death (HR 4.1, p = 0.25), whereas continued harmful alcohol use was associated with increased risk of death (HR 23.2, p < 0.001) (Figure 1). In multivariable analysis, compared to patients with continued alcohol use, length of post-LT hospital stay (OR 1.11 [per day], p = 0.02), and non-Medicaid insurance (OR = 16.3, p < 0.001) were associated with establishing abstinence after post-LT alcohol relapse.

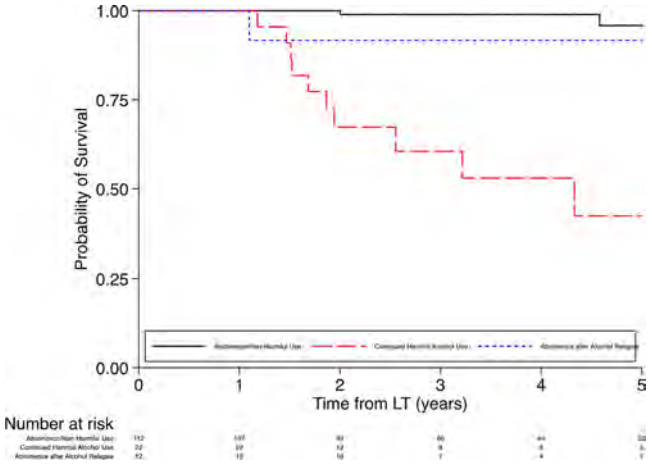

Figure 1. Kaplan-Meier Estimates of Survival in Patients with Abstinence/ Non-Harmful Alcohol Use Post-LT vs. Continued Harmful Use vs. Abstinence after Alcohol Relapse

Conclusion: Re-establishing abstinence after alcohol relapse appears to abrogate the deleterious effects of alcohol use on patient survival after early LT for AH. Our data suggest that encouraging AH LT recipients to enter treatment even after relapse may restore survival.

THU249

Predictors of success in the treatment of anastomotic biliary stricture after liver transplantation

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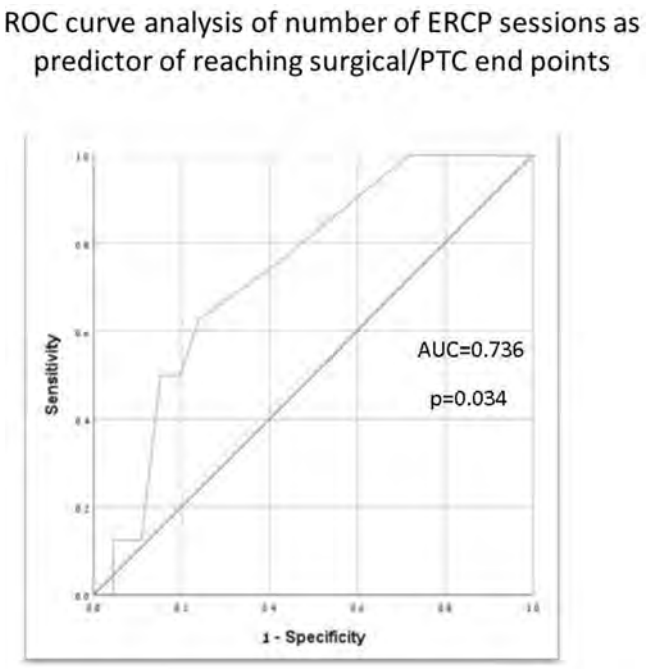
Background and Aims: Anastomotic bile duct stricture is a common complication following liver transplantation (LT). Endoscopic retrograde cholangiopancreatography (ERCP) is first-line choice for diagnosis and treatment of this complication, followed by percutaneous transhepatic cholangiography (PTC) or surgery in case of failure. We aimed to determine the effectiveness and safety of ERCP for anastomotic biliary strictures, and find predictors of ERCP treatment failure and complications.

Method: A retrospective cohort study; demographic, clinical data, number of ERCP sessions, number and type of stents, need for PTC or surgery, complications and mortality were recorded.

Results: Out of 242 patients that underwent LT between 2003–2019 sixty nine patients underwent ERCP, in 54 of them biliary stricture was diagnosed. Median time from LT to ERCP was 54 days (IQR 16–227.5). Overall, 223 ERCPs were performed, with an average of 4.1 ± 3.7 sessions per patient until resolution of stenosis or switch to other treatment modality. In 32 patients (59.2%) ERCP was definitive treatment, 8(14.8%) required PTC or surgery and 9(16.6%) died with stent in place. Five patients (9.2%) are still in treatment. Roc curve analysis has shown that need for more than four ERCP sessions predicts reaching of PTC/surgery end point with 75% sensitivity and 59% specificity (Figure). Fourteen (25.9%) patients developed complications (pancreatitis (12.9%), cholangitis (14.8%) and bleeding (1.8%)).



Plastic, metal or plastic followed by metal stent on the next sessions were used in 40(74.1%), 4(7.4%) and 10(18.5%) patients respectively. No correlation between stent characteristics and outcome or development of complications was found.

Metal stents were introduced in the routine use in 2013. Patients were divided into 2 groups, before and after 2013 (27(50%) in each group). The outcomes in both groups were similar, but patients in the latter group underwent significantly less ERCPs to get outcome (p = 0.03 for cut off 4 or less ERCPs).

Conclusion: Our experience confirms that ERCP is highly effective and safe treatment for anastomotic biliary strictures after LT. We demonstrated that performing more than 4 ERCPs had no added benefit and was significant predictor of need for surgery/PTC. Increased center experience in the recent years resulted in reaching the same outcomes in less ERCP sessions. Prospective data collection is needed to evaluate possible advantages of different type of stents.

THU250

Survival after liver transplant in recipients of different age groups: a systematic review and meta-analysis

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Background and Aims: An increasing number of elderly patients are undergoing liver transplantation for end-stage liver disease and hepatocellular carcinoma. However, there is a paucity of data on the risk of mortality post-liver transplantation with respect to increasing age.

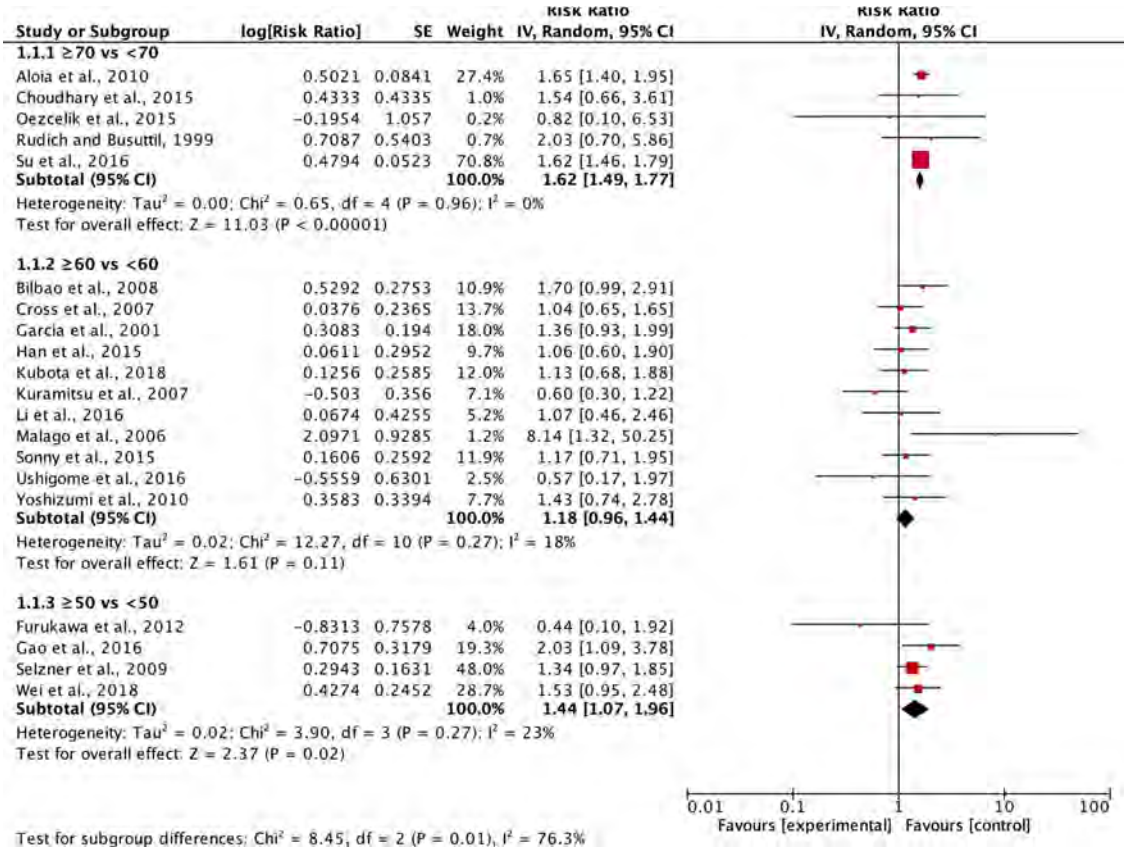

Figure: (abstract: THU250)

Method: We performed a systematic review and meta-analysis to assess the effect of older age on mortality after liver transplantation. A comprehensive literature review was conducted utilizing the PUBMED, MEDLINE, SCOPUS and EMBASE databases through July 2019 to identify all cohort studies that compared the long-term survival outcome between patients who underwent liver transplantation at the age of older recipients versus younger recipients. Effect estimates from each study were extracted and combined using the random-effect.

Results: Of 686 potentially eligible articles, a total of 20 studies with 19,412 participants fulfilled the eligibility criteria and were included in the meta-analysis. With respect to transplant mortality, subgroup analysis showed age ≥70 years compared to younger recipients had the pooled RR of 1.62 (95% CI, 1.49–1.77, $p < 0.0001$) (Figure); age ≥60 years compared to younger recipients had the pooled RR of 1.18 (95% CI, 0.96–1.44, $p = 0.11$) and age ≥50 years compared to younger recipients had the pooled RR of 1.44 (95% CI, 1.07–1.96, =0.02) (Figure). Between-group comparisons, recipients age ≥70 years were significantly increase risk of mortality post-liver transplantation ($p =$ 0.01).

Conclusion: There was a significantly increased risk of mortality post-liver transplantation among recipients age ≥70 years. This suggests that the age of 70 years could be the deflection point where the rate of mortality starts to accelerate, with risks outweighing benefits beyond this age group.

THU251

Prophylactic rifaximin use in liver transplant candidates is associated with false positive results of the alcohol biomarker, ethyl sulphate

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Background and Aims: A key component during assessment for liver transplantation (LT) is assessment of alcohol use and abstinence. LT candidates can be toxicologically screened for the direct alcohol metabolites, ethyl glucuronide (ETG) and ethyl sulphate (ETS). At King's College Hospital, we observed ETS results that provided an anomaly to the reviewed literature which we described as "weak positive" ETS. We sought to explore this discrepancy.

Method: A cross-sectional study reviewed demographic, clinical and laboratory data, including medications. We studied 243 patients who were assessed for LT from December 2017 – November 2018 and provided a urine specimen analysed for ETG/ETS. Chi-square tests of association measured crude relationships between categorical status of urine specimen results and highlighted medications, and multiple logistic regression assessed relationships adjusted for potential confounding variables.

Results: Majority of patients were male (60%) with mean age of 52 years. Aetiology of liver disease was mainly alcohol-related liver disease (34%), non-alcoholic steatohepatitis (16%) and viral hepatitis

(8%). Of the 243 patients, 67% had negative urine ETG/ETS, 7% were positive for both ETG/ETS and 26% were positive for only ETS which was the anomalous result further explored. No samples were ETG positive/ETS negative.
Quantification of the ETS positive/ETG negative results found a mean result of 313 µg/L and median 228 µg/L. The positive range for ETS is 100 µg/L – >80,000 µg/L. We defined these results as "weak positive" ETS.
When comparing the study variables using chi-square tests and multiple regression analyses, only one association was significant. "Weak positive" ETS was strongly associated with concurrent Rifaximin therapy ($p < 0.001$) even after adjusting for Lactulose co-therapy ($p < 0.001$).
Conclusion: During LT assessment, urinalysis for ETG and ETS provides objective evidence of recent alcohol use. Reliability is important given the implications of false positive (or negative) results. Caution should be applied in interpreting urine ETG/ETS results in patients treated with Rifaximin, given the high probability of an anomalous "weak positive" ETS result, which may be falsely interpreted as evidence of covert drinking. We hypothesise that this finding is driven by alterations in the microbiome and the ability for bacteria to degrade urinary ETG but not ETS as is reported in the literature, with Rifaximin modulating this effect.

THU252
Predictive factors of symptomatic nodular regenerative hyperplasia after liver transplantation
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Background and Aims: In the context of liver transplantation (LT), nodular regenerative hyperplasia (NRH) could occur on the graft, responsible for portal hypertension that may lead to death or re-transplantation. To date, no study specifically focuses on predictive factors of events due to NRH. The primary objective of this study is to identify predictive factors of symptomatic NRH after LT.
Method: In this monocenter retrospective study, inclusion criteria were: liver transplant recipients > 18 years (y) and a diagnosis of histologically proven NRH on the graft. All biopsies showing NRH after LT were collected from 2008 to 2018. Patients with NRH recurrence were excluded. Symptomatic forms of NRH were defined as the presence of ascites, esophageal varices with or without bleeding, hepatic encephalopathy, portal thrombosis, retransplantation or death related to NRH.
Results: 115 patients were included. The mean follow-up between LT and diagnosis of NRH was 7.5 ± 8.6 y. The mean age at diagnosis was 53 ± 14 y. Main indication of LT was alcoholic cirrhosis (16.1%). Symptomatic form occurred in 27(23.1%) patients. Symptoms were 18(15.3%) ascites occurrence, 12(10.2%) esophageal varices and 7 (5.9%) variceal bleeding, 3(2.5%) hepatic encephalopathy and 8(6.8%) portal thrombosis. The meantime to onset of symptoms was 1.3 ± 2.9 y after diagnosis. Seven (6%) patients were treated with portocaval shunt including 6 TIPS procedure with a meantime of 0.7 ± 1.9 y after diagnosis. Six (5.2%) and 4(3.5%) patients were retransplanted or died for symptoms related to NRH. Overall survival was 71% versus 92% ($p = 0.012$) and graft survival was 51% versus 89% ($p < 0.0001$), between groups with or without symptoms related to NRH, respectively. In multivariate analysis, the factors associated with symptomatic NRH were low hemoglobine level at diagnosis (OR 0.68, IC95%, $p = 0.027$)) and the ratio spleen size at diagnosis/spleen size before LT (OR 9.57, IC95%, $p = 0.039$).
Conclusion: NRH after LT is a serious condition that leads to symptomatic portal hypertension in 23.1% of patients. Although overall prognosis is good, symptomatic patients experienced significantly lower transplant free survival. Patients who have an increase in spleen size or decrease of hemoglobin rate should be strongly monitored to symptomatic NRH.

THU253
Transplanting livers from hepatitis C positive donors: is it worth the risk?
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Background and Aims: Before the introduction of Direct-Acting Antivirals (DAAs), only selected organs from Hepatitis C virus (HCV) positive donors were successfully transplanted into HCV positive recipients. Since HCV infection is now curable in a large percentage of cases (>95%) it may be possible to transplant organs from HCV positive donors to HCV negative recipients. In this study we aim to analyse current utilization of livers of HCV positive donors in the Eurotransplant (ET) region and its future potential.
Method: All reported post-mortem organ donors with age ≥16 years in the ET region between January 2007 and December 2018 were included. Donors from outside the ET region were excluded. Segmental liver transplantations were excluded as well. First, donor demographics were evaluated for all reported donors by HCV status. Then, utilization and graft survival were analysed for both groups.
Results: A total 22,474 donors were reported in the ET region and 287 (1.3%) donors were tested positive for HCV antibodies (ab), with a range of 0.0–1.7% per country in the ET region. A total of 141 (49%) livers of the HCV ab positive donors were transplanted, 74/141 (53%) in HCV ab positive recipients. Graft failure occurred in 25/141 (18%) recipients directly or later after transplantation. In 5/141 (3.5%) it was due to recurrence of HCV. Of the 21,998 HCV ab negative donors 17,745 (81%) livers were transplanted, 2,245/17,745 (13%) in HCV ab positive recipients. In 2,585/17,745 (15%) recipients graft failure occurred directly or later after transplantation. Recurrence of HCV as cause of graft failure was in 77/17,745 (0.4%) of the recipients with graft failure.
Conclusion: Liver utilization is much higher in HCV ab negative donors as compared to HCV ab positive donors. However, graft failure overall and specifically due to HCV infection occurs in 18% and 3.5% respectively in the HCV ab positive donors. Therefore, the absolute risk is slightly higher in recipients of a HCV ab negative graft. Although the number of HCV ab positive donors is not very high in the ET region, with the new DAAs there is an opportunity to improve utilization of HCV ab positive donors and outcome after liver transplantation. With the increasing waiting lists and relatively stable number of donors, transplant centers should consider all liver grafts of HCV positive donors for transplantation.

THU254
Long-term outcomes of persistently positive hepatitis B surface antigen after liver transplantation for chronic hepatitis B
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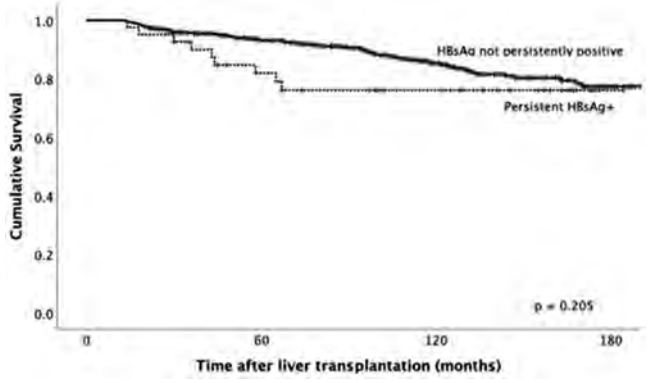
Background and Aims: Antiviral therapy alone without hepatitis B immune globulin (HBIG) has been shown to be effective after liver transplantation for chronic hepatitis B (CHB). However, a small proportion will have persistently positive hepatitis B surface antigen (HBsAg), of which the long-term outcome is unclear. We aim to determine the long-term outcome of recipients with persistently positive HBsAg.
Method: Consecutive patients with CHB and liver transplantation from January 2003 to December 2017 were considered. All patients received HBIG-free regimen as prophylaxis with oral antiviral therapy alone. Graft survival and outcome were determined.
Results: A total of 630 CHB patients were transplanted, of which 582 (92%) had over one year of follow-up and were included. Of these, 486 (84%) were male, and 250 (43%), 212 (36%), and 120 (21%) were transplanted for decompensated cirrhosis, hepatocellular carcinoma (HCC), and severe flares respectively. The median follow-up was 104 months (range, 13–199). Forty-one (7%) had persistently positive HBsAg without evidence of seroclearance, with higher rates observed in severe flares compared to cirrhosis and HCC patients (13.3% vs. 6.8% vs. 3.8% respectively, p = 0.005). The graft survival for persistently positive HBsAg was 81.9%, 76.1% and 76.1% at 5, 10, and 15 years post-transplant respectively, compared to 93.1%, 85.3% and 77.3% respectively for those patients that were not persistently positive for HBsAg (p = 0.205), as shown in the figure. There were 9 graft losses during the follow up period for persistently positive HBsAg patients, of which 4 were due to HCC recurrence, 2 from lymphoma, 2 from extra-hepatic malignancies, and 1 from sepsis. There were no cases of graft loss due to *de novo* HCC or reactivation of hepatitis B virus infection. At the time of last follow-up, all active patients had undetectable HBV DNA.



Conclusion: Despite a persistently positive HBsAg after liver transplantation for CHB in patients receiving HBIG-free prophylaxis, there was excellent long-term graft survival, which was comparable to patients who had evidence of HBsAg loss. Importantly, there was no graft loss from *de novo* HCC or hepatitis B reactivation in persistently positive HBsAg patients.

THU256
NASH is the leading indication for liver transplantation in elderly patients

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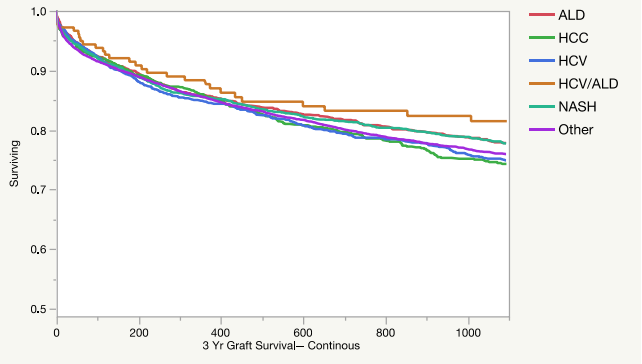
Background and Aims: Non-alcoholic steatohepatitis (NASH) is an increasingly prevalent cause of end-stage liver disease (ESLD) and indication for liver transplantation (LT) in the United States and around the world.
Method: United Network for Organ Sharing (UNOS) databases for waitlisted and transplanted patients were evaluated between 2006 and 2018. Pediatric patients (<18 years old) were excluded. Elderly recipients defined as ≥ 65 years old. Chi-square and Wilcoxon rank-sum analyses were used to compare groups. Logistic regression analyses were performed to assess likelihood of transplantation with odds ratios (OR) and 95% confidence intervals (CI) reported. Three-year graft survival was assessed with Kaplan-Meier (KM) survival analysis. P-values <0.05 were considered significant.
Results: 129,839 patients were waitlisted for LT during the study period, of which 22,897 (14.9%) had NASH as primary diagnosis. Patients waitlisted with NASH were the oldest (median 60 years, IQR 54–65 years, p < 0.0001), and predominantly male (n = 12,091, 50.7%). NASH became the most common primary diagnosis amongst candidates ≥ 64 years old, at which point it accounted for 25.6% of waitlisted patients. Interestingly, NASH was the most common primary diagnosis amongst waitlisted women ≥ 60 years old, while in in men it did not become the most common until ≥ 70 years old. The median age at transplant for candidates with NASH was 64 years (IQR 59–67 years). NASH became the most common diagnosis amongst transplanted recipients ≥ 62 years old (≥59 years old in women and ≥ 69 years old in men). Multivariable analysis showed that patients with NASH were more likely to be transplanted than those with HCV (OR 1.13, 95% CI 1.09–1.18, p < 0.001) and ALD (OR 1.06, 1.01–1.11, p < 0.001). Amongst elderly recipients, patients with NASH were more likely to be transplanted than those with HCV (OR 1.13, 1.07–1.18, p < 0.001), but there was no difference between NASH and ALD (OR 1.03, 0.99–1.09, p = 0.15). KM survival analyses showed no difference in 3-year graft survival across etiologies of ESLD overall, or amongst elderly recipients alone (Figure 1).



Conclusion: NASH is the most common indication for waitlisting and transplantation in elderly patients. Despite being a disease of the elderly, there is no difference in graft survival amongst recipients with NASH.

THU257
Hepatitis B immunoglobulin prophylaxis for prevention of de novo Hepatitis B infection from hepatitis B core antibody-positive donors

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Background and Aims: Recently, hepatitis B core antibody (anti-HBc) positive liver grafts are used as extended criteria donor organs. However, prophylaxis methods to prevent de novo hepatitis B virus (HBV) infection after liver transplantation (LT) are still controversial. Thus, the purpose of our study is to evaluate the risk and outcomes of

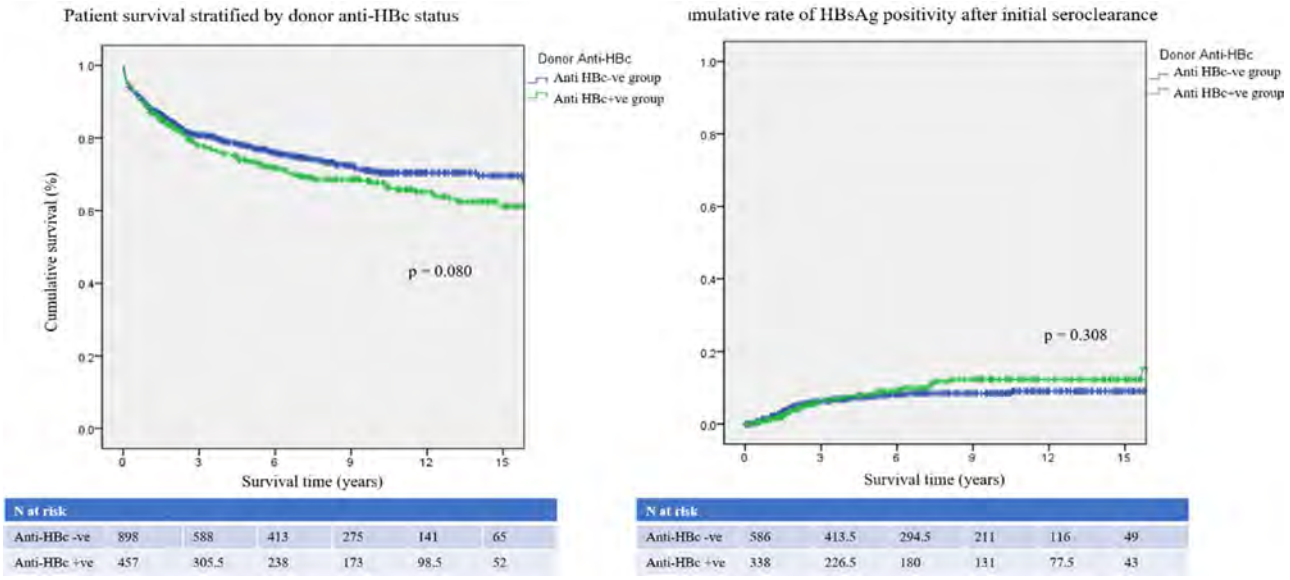

Figure: (abstract: THU257)

receiving anti-HBc positive grafts with prophylactic HBIG monotherapy.

Method: All adult patients who underwent LT at Samsung Medical Center in Seoul, Korea, between January 2001 and December 2018 were gathered from a prospectively maintained database and reviewed retrospectively. HBV patients received the combination treatments with antiviral prophylaxis and hepatitis B immunoglobulin (HBIG). Prophylactic HBIG monotherapy was given for patients without HBV receiving grafts from anti-HBc positive donors.

Results: A total of 1355 patients underwent LT during this period. Among them, 457 (33.7%) were anti-HBc positive and 898 (66.3%) were anti-HBc negative donors, who underwent follow-up for a median time of 5.7 years. Perioperative outcomes (mortality in 30 days, complications and postoperative ICU stay period) were similar between the two groups. Also, there were no significant difference in the 1-, 5-, 10- and 15-year patient survival rates between the anti-HBc positive (87.5%, 73.5%, 67.7% and 61.2%) and the anti-HBc negative groups (88.5%, 77.7%, 70.7% and 69.6%, p = 0.080). All of the 117 recipients who were HBsAg negative and received anti-HBc positive grafts were given prophylactic HBIG monotherapy. Only one patient (0.9%, 1/117) developed de novo HBV during follow-up. There were 972 HBsAg-positive patients and 348 (35.8%) received anti-HBc positive grafts. The risk of HBV recurrence was similar between 2 groups (p = 0.308). The donor anti-HBc status did not have a significant influence on the long-term survival or the risk of de novo or recurrent HBV infection after LT.

Conclusion: De novo HBV was very rare especially with HBIG prophylaxis in non-HBV patients received anti-HBc positive liver graft. There was no significant influence of anti-HBc positive grafts on the perioperative and long-term outcomes after LT.

THU258

Improved patient and graft survival from kidney transplantation in liver transplants for congenital hepatic fibrosis and Caroli's disease

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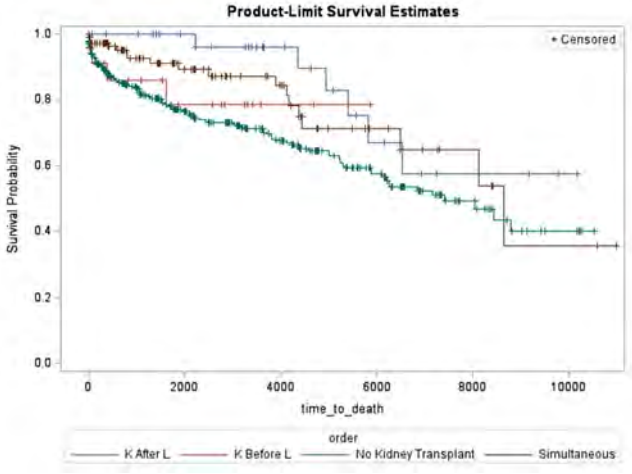
Background and Aims: Congenital hepatic fibrosis (CHF) and Caroli's disease (CD) have a common etiology, arising as ductal plate malformations, and can include autosomal recessive polycystic kidney disease. The natural history of the liver disorders either alone or in combination appears highly variable with little data on outcomes, particularly in liver transplantation. We aimed to determine whether there are differences in patient survival and graft failure between patients with CHF and CD after liver transplantation and how this is impacted by kidney disease leading to kidney transplantation.

Method: We evaluated liver transplant outcomes of CHF versus CD, from 1987 to 2018, using the entire United Network of Organ Sharing dataset that incorporates transplantation in the United States. Using standard software, data are presented as mean + standard deviation or median and analysed with the student t test and Chi square. Kaplan-Meier curves were constructed, and log-rank tests were applied to test for differences in graft failure and patient survival. A $p < 0.05$ was considered statistically significant.



Results: A total of 626 unique patients diagnosed with either CHF, n = 363, CD, n = 243 or both diagnoses, n = 20 were identified from the SRTR data. Patients with CHF were primarily transplanted as children

or young adults while the CD group is evenly spread throughout the age groups. This resulted in a difference of 24 years in the median age (16 years versus 40 years) at transplantation (p = 0.000). There was also differences amongst racial groups with black patients being twice as common in the CD as compared to the CHF group (p = 0.013). There was a statistically significant difference in patient (p = 0.020) and graft survival (p = 0.003) between patients with CHF versus CD. A total of 305 kidney transplants were performed in 235 individuals with either CHF or CD;172 received 1 graft, 56 received 2 grafts and 7 received 3 grafts. Patient survival was better with simultaneous (p = 0.020) and kidney transplant after liver transplant (p = 0.034), Figure 1. Liver graft survival was significantly better with simultaneous liver and kidney transplant (p = 0.015). Multivariate analysis confirmed age, race, CHF versus CD and simultaneous kidney transplantation as significant for graft survival; The same factors were also significant for patient survival apart from simultaneous kidney transplantion.

Conclusion: Patients with CHF and CD, although related etiologies, have diverse outcomes for liver transplantation. Patients with CD undergo liver transplantation across wider ages than CHF patients. CD patients have worse graft survival and higher rates of death than CHF patients. Both groups of patients benefit from kidney transplantation either simultaneously or following liver transplantation.

THU259

Outcomes of liver transplantation for metabolic disorders in children

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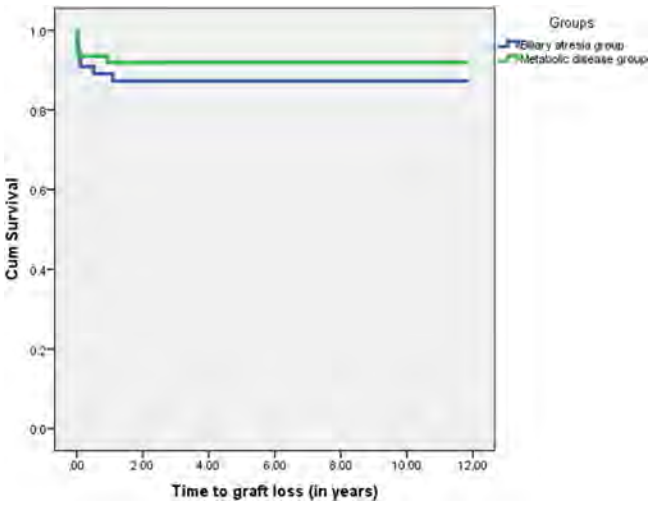
Background and Aims: The main indication for liver transplantation (LT) in children has been biliary atresia. Recent advances in surgical management and the development of new immunosuppressants have made LT a viable therapeutic option for an increasing number of disorders in this modern era. In particular LT has become an effective therapeutic modality for patients with metabolic liver diseases, especially urea cycle disorders. To be considered a treatment of choice for metabolic patients, LT must have at least equivalent outcomes to biliary atresia. As a large center for LT for metabolic disorders we are able to examine this issue.

Method: This was a retrospective analysis comparing between isolated pediatric liver transplantation for metabolic liver diseases (N = 62) versus biliary atresia (N = 55) in the period between January 2008 and December 2018. Standard statistical software was used. Proportions are compared using chi-square and continuous variable using student t-test. Kaplan-Meyer curves are constructed and compared using the log-rank test.

Results: The median age for the metabolic group was 2 (0.16–16) year versus 1 (0.4–15) year for the biliary atresia group (P = 0.0001). 41.9% were female in metabolic group versus 73.6% in biliary atresia group (P = 0.001). 14.5% were African American in the metabolic group versus 41.5% in biliary atresia group (P = 0.010). Graft types included whole liver, cadaveric split liver, living donor segmental liver (54.8%, 38.7%, 6.5% in the metabolic group versus 40%, 27.3%, 32.7% in the biliary atresia group, P = 0.001). The 1-, 3-, and 5-year patient survival for the metabolic group were identical to the biliary atresia group (95%, 95%, and 95%). The 1-, 3-, and 5-year graft survival for metabolic group was 92%, 92%, and 92% versus 87%, 87%, and 87% for the biliary atresia group (P = 0.418). Postoperative complications included biliary (14.5% in metabolic vs. 33.3% in the biliary atresia group, P = 0.017), vascular (19.4% in the metabolic group vs. 35.8% in the biliary atresia group, P = 0.047), postoperative bleeding (16.1% in metabolic group vs. 20.8% in the biliary atresia group, P = 0.522). High grade Clavien-Dindo (3B or higher) complications were significantly less in the metabolic group (25.8% vs. 48.1% in the biliary atresia group, P = 0.014). Acute rejection tended to be higher in metabolic group (37.1% versus 21.8% in the biliary atresia group, P = 0.072).



Conclusion: Pediatric liver transplantation for metabolic liver diseases in our high volume center has excellent outcomes in comparison to biliary atresia. It has similar patient and graft survival but with less postoperative complications and readmissions. Rejections tended to be higher in metabolic group.

THU260

Assessment of long-term risk of cardiovascular disease after liver transplantation

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Background and Aims: The risk of cardiovascular disease (CVD) is increased in people who have undergone liver transplant (LT) and is a common cause of death in long-term follow-up studies. Risk assessment for CVD is commonplace in non-transplant cohorts but the relevance of commonly used systems of CVD risk scores in the UK have not been evaluated in liver transplant patients. This is important as accurate risk assessment can guide interventions to reduce cardiovascular risk such as statin therapy. We evaluated the accuracy of Q-RISK, Framingham-CVD and the BNF scores in a cohort of patients in Leeds.

Method: All patients who had undergone a first liver-only transplantation in Leeds from 2008–2012 were identified from a prospectively maintained database. Those patients over 25 and surviving for at least 1 year after LT were included. Baseline characteristics were noted and information about clinical outcomes was extracted from clinical notes. CVD that occurred after the first year of follow-up were noted to exclude peri-operative events. Ten-year risk scores for CVD were calculated at 12 months after LT. Test accuracy was assessed with receiver-operator curves using the "pROC" package in R.

Results: In total (367–36 deaths – 16 under 25) 315 patients were included with a maximum of 10.6 years follow-up (median 7.2 years, IQR 5.5–8.4 years). After the first year of follow-up, there were 27 patients with incident CVD (8%) – of which one event (a myocardial infarction) was fatal – giving a crude event rate of 1.1%/year. At twelve months after LT, median CVD risk scores were: Q-RISK 2 8.8 (IQR 3.5–14.4), Framingham CHD 3.4 (1.2–7.3) and BNF 2.8 (1.0–6.1). The Q-RISK score had the best performance: AUROC 0.72 (95%CI 0.62–0.82) followed by the Framingham CHD score, AUROC 0.70 (95% CI 0.61–0.79) and the BNF score, AUROC 0.69(95% CI 0.60–0.78).

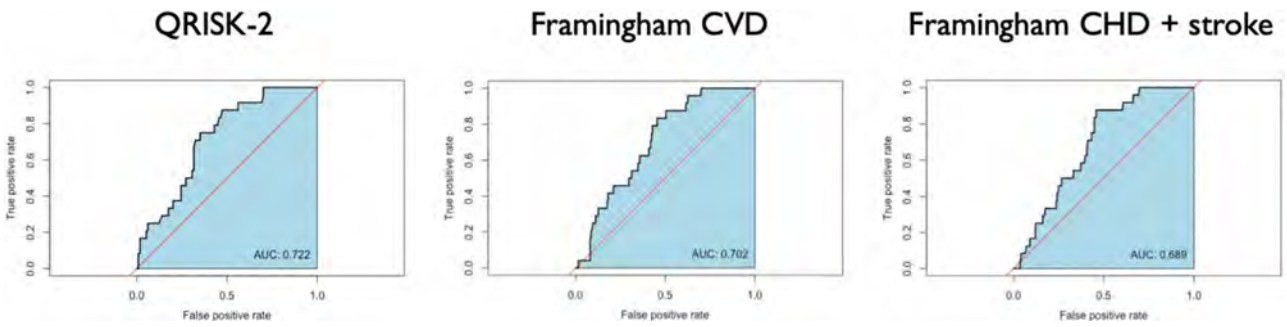

Figure: (abstract: THU260)

Conclusion: cardiovascular disease in this cohort was not a common event and was usually not fatal. The scarcity of CVD events limits this analysis. However, the Q-RISK score, recommended by NICE for non-transplant populations, was the most accurate score to predict incident CVD events.

THU262

Portal venous thrombosis and liver transplant: incidence and evolution in the 1st year after transplant

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Background and Aims: Portal venous thrombosis (PVT) occurs, before and after liver transplant. There are a few studies about it. We do not know its incidence and evolution in our hospital. To determine the incidence of pre and post-transplant PVT and describe: patient characteristics, donation type, predisposing factors, treatments and mortality.
Method: It is a retrospective observational study, where we include patients who received liver transplant from 2010 to April 2019 in our center. We selected patients with pretraplant PVT diagnosed by imaging tests (Eco-Doppler, abdominal Angio-CT) and/or intraoperative diagnosis. In the post-transplant follow-up was with Eco-Doppler: 1st week and 1st, 3rd and 12th month. The clinical and demographic characteristics of the patients, type of donor, smoking, predisposing factors (atrial fibrillation, Phospholipid Syndrome), pre-transplant and post-transplant treatment, post-transplant PVT and mortality in the 1st post-transplant year were collected.
Results: 278 patients were transplanted, 65 (23%) had pre-transplant PVT. Of these, 55 were men (85%) and 10 women (15%). The average age was 56 + –8.4 years. 43% (n: 28) were non-smokers, 31% (n: 20) ex-smokers and 26% (n: 17) smokers. 94% (n: 61) had no predisposing factors and 6% (n: 4) did. 98.5% (n: 64) was a cadaveric donation and 1.5% (n: 1) asystole. The pre-transplant diagnosis was 100% (n: 65) by Eco-Doppler. 78.5% (n: 51) presented intraoperative thrombosis. 68% did not receive pre-transplant treatment and 32% did. Postransplant PVT diagnosed by Eco-Doppler was 15% (n: 10), 12% (n: 5), 8% (n: 5) and 4% (n: 3), in the 1st week, the 1st month, 3rd month and 12th month, respectively. 89% received anticoagulation after transplant. Eight patients died (12%).
Conclusion: The incidence of pre-transplant PVT was high (23%). Few patients had predisposing factors (6%) and most (57%) had been or were smokers. All patients received anticoagulation after transplant and 89% maintained it until the first year. The incidence of post-transplant PVT was low (4%) with a good response to anticoagulation (89%). Mortality in the 1st year was not related to PVT.

THU263

Utility of anticoagulation in portal venous thrombosis before and after liver transplant

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Background and Aims: Portal venous thrombosis (PVT) is a relatively common complication of liver transplant. Its prophylaxis with anticoagulants is a controversial issue currently. The objective of these work was to determine the efficacy of anticoagulation in PVT, before and after transplant, as prophylaxis in relapse of PVT.
Method: Our study included 278 patients undergoing liver transplant from January 2010 to April 2019 in our center. 65 patients with pretraplant PVT diagnosed with imaging tests (Eco-Doppler/Angio-CT) or during surgery were selected. Patients without contraindications received anticoagulation (vitamin K antagonists (VKA)/Low molecular weight heparin (LMWH)) until surgery. After this, all patients received anticoagulation (VKA/LMWH) for 6 to 12 months. Ultrasound control was performed at the 1st week and at the 1st, 3rd, and 12th month post-transplant.
Results: 23% (n: 65) of the patients had PVT before transplantation. 32% (n: 21) of these received pre-transplant anticoagulation, 15% (n: 10) with HBMP and 17% (n: 11) with VKA. In treated and untreated patients, intraoperative thrombosis was 52% (n: 11) and 91% (n: 40), respectively. Only 3 patients treated (4.6%) had hemorrhagic complications. 11% of patients (n: 7) did not receive early post-surgery anticoagulation, by contraindication, the rest 89% (n: 57) did. The overall recurrence of PVT in the 1st year was 4% (n: 3). Post-transplant recurrence of PVT was 2.5% (n: 2) in patients with LMWH and 1.5% (n: 1) in patients with VKA.
Conclusion: Our study concludes that those patients with pre-transplant PVT who received anticoagulant therapy prior to surgery had a considerable reduction in the rate of intraoperative thrombosis with respect to those who did not receive it. In turn, the number of hemorrhagic complications was very low and without fatal consequences in any case. The overall recurrence rate in the post-transplant in the first year was less than 5%, being lower in those patients who received anticoagulant therapy, therefore, our study demonstrates the efficacy of post-transplant anticoagulation to prevent recurrence.

THU264

Safety and efficacy of a cardiac risk stratification protocol based on traditional cardiac risk-factors in patients undergoing liver transplantation

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Background and Aims: Coronary artery disease (CAD) is prevalent in patients undergoing liver transplantation (OLT) and confers an increased peri-operative risk. Routine screening for CAD is recommended however data on the effectiveness of screening strategies is limited. We aimed to assess the safety and efficacy of a 3-tiered cardiac risk-assessment protocol that stratifies patients based on age and traditional cardiac risk factors (RF).
Method: Consecutive patients >18 years old undergoing OLT assessment were prospectively included from 2010 to 2017. Patients receiving multi-visceral transplant were excluded. Patients were stratified into one of 3 risk groups and received standardised investigations (Table). Primary outcome was peri- or post-operative cardiac events.
Results: 586 patients undergoing 606 OLT assessments were included. Median age was 56 years (IQR 48–60), 70% were male and median MELD score was 18 (IQR 13–25). Common indications for OLT were hepatitis C, alcohol and hepatocellular carcinoma. Cardiac RFs included: diabetes (27%), smoking (50%), hypertension (17%), hypercholesterolemia (8%), family (17%) or personal (6%) history of heart disease and obesity (28%). 61% patients had ≥2 risk factors.
80 patients were identified as low risk (LR), 269 intermediate risk (IR) and 257 high risk (HR). 11 patients were rejected following cardiac assessment: 1 LR patient (abnormal ECHO with pulmonary hypertension (PHT) at CA); 2 IR patients (cardiac amyloid and cirrhotic cardiomyopathy), and; 8 HR patients (aortic stenosis, PHT, cardiomyopathy [n = 2], multi-vessel CAD [n = 4]). Peri-operative cardiac events were observed in 8 patients (event rate 1.3%) with 2 deaths (0.3%). 4 cardiac events occurred in the IR group (Non-ST elevation myocardial infarction (NSTEMI) [n = 3], death from progressive right ventricular dysfunction post reperfusion) and 4 in the HR group (NSTEMI [n = 3], death post-operatively from cirrhotic cardiomyopathy).
Conclusion: Cardiac risk stratification based on traditional cardiac RFs with the selective use of DSE, CA and CTCA is a safe and feasible approach that results in a very low peri-operative cardiac event rate.

THU265

Projection of liver transplant activity per indication in France and United Kingdom

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Background and Aims: Efforts towards eliminating hepatitis C virus (HCV) are likely to yield many patient relevant benefits and cost savings for health services. As another externality, decreasing numbers of people with HCV subsequently decreases the demand for liver transplantations (LT) due to HCV. The reductions in HCV indicated LT will make more livers available for other indications. In this analysis changes in LT were projected based on current trends to explore which liver failure conditions may benefit from eliminating HCV.
Method: The number of new registrants and first LTs per indication were identified from annual reports of the French and UK LT registries. Data were available from 2013–2018 for both countries. The proportional change in LTs was calculated per year and averaged across all years. Projections were made based on the mean proportional change within each indication with non-zero values until HCV-related first LTs constituted <1% and ≤0.5% of the dataset. The number of LTs for benign tumors were projected to increase by 2 biennially based on observed trends.
Results: Incidence-specific values were available for the full French registry; and for elective deceased donor liver only transplants for the UK. The frequency of HCV-related elective first LTs decreased to <1% and ≤0.5% by 2024 and 2026 in France; and by 2022 and 2024 in the UK. The number of LTs related to alcoholic liver disease were projected to decrease in France and increase in the UK. In both countries LTs increased noticeably for HCC and other malignant tumors, other causes of cirrhosis and pathologies. Metabolic diseases preceded first LTs with increasing numbers in the UK. In France, the proportion of patients receiving LTs to the number of registrants was higher by the end of 2018 in contrast to 2013 for HCV, other malignant tumors, sclerosing cholangitis, autoimmune cirrhosis, other causes of cirrhosis and pathologies.
Conclusion: The dynamics of receiving LTs has altered substantially with the availability of highly curative therapies for HCV. In both countries targets to eliminate HCV as an indication for LT were achieved within 8 years; leading to a higher transplantation rate and possibly shorter waiting times for indications beyond cirrhosis. The growth seen in these indications and existing waiting lists provide further motivation towards HCV elimination.

THU266

The impact of gender and comorbidity burden on liver transplant eligibility and patient survival

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Background and Aims: Disparity is reported in liver transplant (LT) waitlist mortality for females, however the reasons are not elucidated. Gender based differences in medical comorbidities have been described, but the impact of comorbidity burden on LT-free survival, LT eligibility and post-LT survival is unquantified. We aimed

Table: (abstract: THU264): Three-tiered cardiac risk stratification protocol

Risk group	Investigations	Results
Low -Age<45 *OR* Diabetic age<35 *AND* -No cardiac RF	Trans-thoracic ECHO	Normal: No further investigation (NFI) Abnormal: high-risk Cardiology clinic
Intermediate -Age>45 *OR* Diabetic age 35–50 *OR* -History of heart disease *OR* -Males >35 with 1 additional cardiac RF	Dobutamine Stress ECHO (DSE)	Normal: NFI Abnormal: Coronary angiogram (CA)
High -Age>60 *OR* Diabetic age>50	DSE	Normal: CT coronary angiogram (CTCA) Abnormal: CA

Table: (abstract: THU266)

	Univariable analysis		Multivariable analysis	
Factor	Hazard ratio (95% confidence interval)	P-value	Hazard ratio (95% confidence interval)	P-value
Analysis of 90-day LT-free mortality				
CCI (reference = 0)				
CCI 1–2	1.6 (0.8–3.4)	0.2	1.8 (0.8–0.1)	0.18
CCI >2	2.2 (0.77–0.2)	0.14	**5 (1.5–6.8)**	**0.01**
Female-gender	**0.42 (0.2–0.97)**	**0.043**	0.8 (0.3)	0.6
Analysis of LT eligibility				
CCI (reference = 0)				
CCI 1–2	**0.45 (0.31–0.67)**	**<0.001**	**0.43 (0.27–0.69)**	**<0.001**
CCI >2	**0.3 (0.14–0.65)**	**0.002**	**0.26 (0.11–0.59)**	**0.001**
Female-gender	0.8 (0.5–0.1)	0.16	**0.4 (0.25–0.67)**	**<0.001**
Analysis of post-LT mortality				
CCI (reference = 0)				
CCI 1–2	1.6 (0.6–4.5)	0.4	1.03 (0.3–3.2)	0.9
CCI >2	**3.7 (1.1–12.6)**	**0.038**	1.5 (0.4–6)	0.5
Female-gender	**2.8 (1.1–6.7)**	**0.028**	2.9 (0.99–8.3)	0.052

to describe the comorbidity burden and its impact on survival and LT eligibility in females and males with cirrhosis.

Method: We reviewed 340 adults with cirrhosis referred to our centre for their first LT in 2012 through initial evaluation, LT selection and long-term post-LT outcomes. The comorbidity burden was assessed using the Charlson Comorbidity Index (CCI), while excluding the liver disease component and hepatocellular carcinoma (HCC) from the CCI. CCI was examined as categories (0, 1–2,>2). Cox proportional hazards analyses for study endpoint were controlled for age, model for end stage liver disease (MELD), race, aetiology of liver disease and HCC.

Results: The 340 patients (37% females) mean age 56 ± 11, and 23% had HCC. Females had lower mean MELD (15 ± 6) than males (17 ± 7), more frequent fatty liver (27% vs. 17%) and less alcohol related disease (24% vs. 30%), but similar age, CCI (0.9 ± 1.1 for both genders), race, BMI, and HCC. CCI was 0/1–2/>2 and 48%/39%/13% in females and 42%/47%/11% in males (p = 0.3). Over a median follow up of 6.5 years (IQR 6 to 6.8) the impact of CCI and gender on; (i) 90-day LT-free survival in 332 patients not undergoing LT within 90 days, (ii) LT eligibility in 177 patients reviewed in LT selection committee after complete evaluation and (iii) 1 and 5-year post-LT survival in 99 patients (median follow up 5 years) was analysed (Table). The risk of LT-free mortality in males was attenuated by CCI and other covariates.

Conclusion: Comorbidity burden is similar in females and males referred for LT and adversely impacts LT-free survival and LT eligibility in cirrhosis. If validated these data may inform mortality-risk modelling in cirrhosis. However, comorbidity burden does not explain gender-based differences in LT eligibility or post-LT survival, and further study is needed to mitigate these disparities.

THU268

Accuracy of triple echo MRI in predicting hepatic steatosis in potential liver donors

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Background and Aims: Living donor liver transplantation is a lifesaving procedure for patients with end stage liver disease and patients with hepatocellular carcinoma especially in regions where there is severe shortage in cadaveric liver grafts. Although there is variability in practice among transplant centres regarding the acceptable cut off value for donor hepatic steatosis, significant hepatic steatosis of >10 to 15% is considered a limitation for donation in many centres since this might affect the transplant outcome. Many centres routinely perform liver biopsy for steatosis quantification prior to transplantation. The goal of this study is to evaluate the accuracy of triple Echo MRI in predicting hepatic steatosis in potential liver donors in comparison to histopathology and if this non-invasive method could replace or limit the need for liver biopsy.

Method: This is a single centre, retrospective study including potential liver donors who underwent triple echo MRI of the liver and liver biopsy between March 2015 to November 2019. Liver fat fraction was measured by triple echo MRI as part of the donor evaluation process and compared to histopathology steatosis. Sensitivity, specificity, positive predictive value and negative predictive value of fat fraction by triple echo MRI were calculated using cut off value of > 10 hepatic steatosis. Correlation between MR fat fraction and histopathology hepatic steatosis was examined by Pearson correlation coefficient.

Results: In the study period, 163 potential liver donors were identified in our medical records. Of these 163, 35 potential liver donors met the inclusion criteria of having both triple echo MRI and liver biopsy were included in the analysis. The mean donor age was 31 years. Out of the 35 donors, 28 were male and 7 were female donors. The average weight and BMI were 71.1 kg and 25.3 respectively. The correlation coefficients of triple-echo MR imaging and histopathological hepatic steatosis was r of 0.860. For Threshold of ≥10% steatosis, triple Echo MR demonstrated sensitivity of 71.43%, specificity 92.86%, positive predictive value 71.43% and negative predictive value 92.86%.

Conclusion: This study demonstrates a good correlation between triple echo MR fat quantification and histopathological hepatic steatosis in healthy liver donors with good performance to exclude significant hepatic steatosis ≥10%. Our results suggest that triple echo MR might be enough for evaluating hepatic steatosis in potential liver donors and potentially might replace or limit the need for liver biopsy.

THU269

Preliminary results of a prospective pilot program for transplantation of patients with alcohol-related liver disease and less than 6 months abstinence

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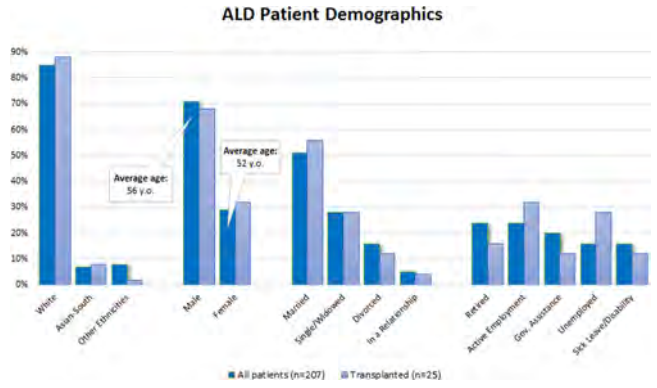
Background and Aims: In Canada, 6 months of abstinence for those with alcohol-associated liver disease (ALD) is typically required prior to being listed for liver transplantation (LT). This policy disadvantages

those who cannot survive this timeframe. The Ontario ALD Pilot Program was initiated in 2018 to provide access to LT for ALD patients through an in-depth examination of alcohol use history, social support and psychiatric comorbidity, as well as the provision of pre- and post-LT relapse prevention therapy.
Method: All referrals were triaged using pilot-specific inclusion criteria. Patients were assessed by a multidisciplinary team, including transplant hepatology, addiction psychiatry, social workers and a nurse practitioner. Random ethyl glucuronide (EtG) testing for alcohol and relapse prevention therapy was performed.
Results: We reviewed 390 referrals from May 2018 to November 2019, with an average NaMELD of 22. From these, 124 referrals (32%) were declined upon initial triage (72 did not meet program criteria, 52 for other reasons). The remaining patients (n = 259) were assessed. The demographic and socioeconomics of them are presented in Figure 1. Of this group, 88 (34%) did not meet ALD inclusion criteria for the following reasons: 72 had severe alcohol use disorder, 17 had a positive urine EtG, 14 had severe psychiatric comorbidity and 14 declined to participate in relapse prevention. Forty-six patients (12%) were listed for transplantation with an average NaMELD of 26. Twenty-five (6.4%) were transplanted, three of whom expired. After an average of 158.6 days post-discharge from hospital, two patients had returned to alcohol use as per positive EtG tests.



Conclusion: The high volume of declined referrals based on history of alcohol use highlight the challenge of assessing ALD patients with less than 6 months abstinence. Based on this complexity, close monitoring of potential relapse post-transplant and the provision of appropriate therapy should be integral part of transplant follow up for these patients.

THU270

Positive complement-dependent cytotoxicity crossmatch results do not influence long-term graft or patient survival following liver transplantation

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Background and Aims: Transplant recipients have typically been screened for the presence of pre-formed anti-donor antibodies with complement-dependent cytotoxicity (CDC) crossmatch testing, prior to kidney and other solid organ transplants. The presence of positive CDC results may guide organ allocation and inform the risk of rejection and immunosuppression choice. There are conflicting reports as to whether CDC crossmatch status is important for outcomes following liver transplantation (LT), hence testing does not routinely alter clinical practice. We aimed to assess whether the presence of a positive CDC crossmatch at the time of LT influenced long term graft outcomes.
Method: We retrospectively identified all LT operations performed at the Royal Free Hospital, London, between October 1999 and December 2016 from the hospital LT database and identified all associated CDC crossmatch assays from laboratory databases. We compared graft outcomes between those with positive and negative crossmatch results.
Results: 1125 LT were identified during the study period; 1076 (96%) LT had an associated CDC crossmatch result available. 84 (7.5%) recipients had a positive T cell CDC crossmatch, 193 (17%) a positive B cell CDC and 204 (19%) were positive for either or both T cell and B cell assays. The presence of a positive CDC crossmatch was more prevalent in female recipients (p = 0.03).
Patients were followed up for a median time of 9 years. Positive CDC crossmatch for T cell only, B cell only or either T or B cell assay was not associated with a greater risk of graft loss over time (log rank p = 0.83, 0.27 and 0.34 respectively). Similarly, the overall hazard of graft loss with a positive T and/or B CDC was not raised (HR 1.22 (95% CI 0.93–1.6, p = 0.15)). There was no increase in the rate of re-transplantation with positive crossmatch (p = 0.75) or for mortality (log rank p = 0.19) with a positive T or B cell CDC.
Conclusion: This large cohort study, reporting over 10,000 patient-years following LT, demonstrates that the presence of a positive CDC at the time of LT was not associated with greater graft loss or patient mortality in the era of modern immunosuppression protocols. Whether these patients are at higher risk for manageable acute rejection episodes or other adverse outcomes remains unclear.

THU271

Pregnancy outcomes after liver transplantation: a systematic review and meta-analysis

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Background and Aims: Liver transplant (LT) remains the gold standard for treatment of end stage liver disease. There is an increasing number of liver transplantation in females of reproductive age. The aim of this study was to conduct a systematic review and meta-analysis to evaluate pregnancy outcomes after liver transplantation.
Method: The MEDLINE, Embase and Scopus databases were searched for relevant studies published through December 2018. Study selection, risk of bias assessment and data extraction were conducted independently by two reviewers. Estimates of pregnancy related outcomes in LT recipients were generated and pooled across studies using the random effects model.
Results: A comprehensive search of the literature identified 1,430 potential studies. Thirty-eight studies with 1,131 pregnancies from 838 LT recipients were included in the analysis. Common LT indications included autoimmune hepatitis, chronic parenchymal diseases and cryptogenic cirrhosis. The mean maternal age at pregnancy was 27.8 years with a mean interval from LT to pregnancy of 59.7 months. The live birth rate was 80.4% with a mean gestational age of 36.5 weeks. The rate of miscarriages (16.7%) was comparable to the general population (10%–20%). The rate of pre-term birth, pre-eclampsia and cesarean delivery (32.1%, 12.5% and 42.2%) among LT recipients were all higher than the rates for the general United States

population (9.9%, 4%, and 32%, respectively). The majority of the analyses were associated with substantial heterogeneity.

OUTCOME	NUMBER OF STUDIES	POOLED ESTIMATE	95% Confidence Interval	I^2
Mean Maternal Age (years)	31	27.8	26.8–28.8	88.4
Mean Gestational Age (weeks)	27	36.5	35.9–36.9	76.4
Mean Interval from Transplantation to Pregnancy (months)	29	59.7	50.7–68.6	95
Maternal Outcomes Rates				
Pre-eclampsia (%)	32	12.5	9.8–15.9	24.5
Cesarean Delivery (%)	34	42.2	35.5–49.2	73
Miscarriages* (%)	37	16.7	12.5–22	58.7
Fetal Outcomes				
Pre-term Birth** (%)	36	32.1	26.8–38	55.6
Mean Birth Weight (grams)	28	2691.9	2574–2809	85.5
Live Births (%)	38	80.4	74.8–85	58.4

*Includes elective abortion, spontaneous abortion, and stillbirth.
**Defined as live birth prior to 37 weeks gestation.

Conclusion: Pregnancy outcomes following liver transplantation are favorable but the risk of some maternal and fetal complications is increased. Large studies along with consistent reporting to national registries is necessary for appropriate patient counseling and to guide clinical management of liver transplant recipients during pregnancy.

THU272

Clostridium difficile infection in liver transplant recipients is uncommon and does not impact long-term survival: a case-control study

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Background and Aims: *Clostridium difficile* infection (CDI) occurs in up to 14% of liver transplant (LT) recipients in the first year after transplantation. There are conflicting data on whether CDI is associated with increased mortality in LT recipients. We aimed to determine the prevalence, risk factors and patient survival associated with CDI in LT recipients.
Method: Consecutive patients who underwent deceased-donor LT from 01/01/2007 to 31/12/2017 were studied retrospectively. All patients received at least 3 days of routine prophylactic antibiotics post-LT. CDI was defined by positive enzyme immunoassay for *C. difficile* toxins A/B performed on diarrhoeal stool within 12 months post-LT. Data were extracted from microbiology and LT databases and medical records. Severity of CDI was defined by Australasian guidelines (Cheng et al. 2011). CDI cases were matched by age, sex, LT indication and year of LT to uninfected controls using a ratio of 1:2. The primary outcome of interest was patient survival.
Results: During the study period, 676 patients underwent LT, of which 32 (4.7%) were diagnosed with CDI. Most CDI cases were male (71.8%) with a median age of 55 years (IQR 51–60) and mean pre-LT MELD of 23 (±8.7). Among CDI cases, the most common LT indications were HCC (28.1%), decompensated cirrhosis from HCV (25.0%) and NASH (18.8%). Baseline characteristics were similar between cases and controls except CDI cases were less likely to receive rifaximin pre-LT (15.6% vs 35.9%, p = 0.04). The median time from LT to CDI was 28 days (IQR 14–65) with most diagnosed in hospital (ward 56.3%, ICU 12.5%, community 31.3%). In 18 (56.3%) cases antibiotics were received within the previous 7 days. There were 3 cases of severe CDI but no CDI-related deaths or colectomies. The majority responded to oral metronidazole alone (71.9%). Single recurrence of CDI occurred in 4 patients, the majority was treated with oral metronidazole alone (75.0%). Patient survival did not differ between CDI cases and controls over a median follow-up of 6.3 years (IQR 3.9–8.0) (Figure). CDI cases were more likely to have returned to theatre post-LT (34.4% vs 15.6%, p = 0.04) and have longer hospital stays after LT (35.0 vs 26.3 days, p = 0.03). Only length of hospital stay after LT was associated with CDI on binary logistic regression (OR 1.03, 95% CI 1.00–1.06, p = 0.02).

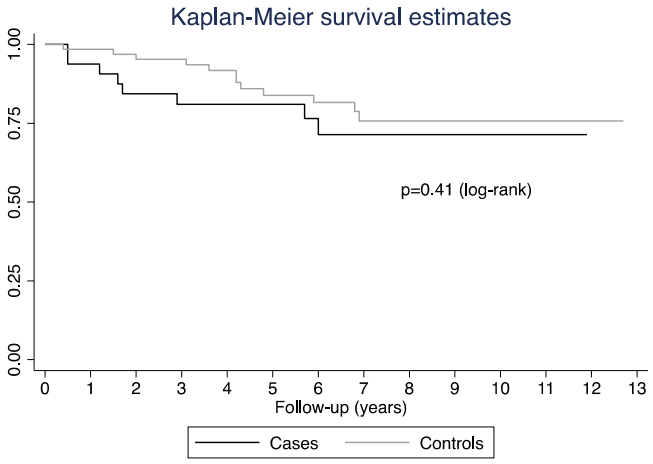

Figure: Post-transplant patient survival among *C. difficile* infection cases and matched uninfected controls

Conclusion: In this single-centre Australian study, CDI within 12 months post-LT was uncommon, of low severity and associated with longer hospital stay after LT. Contrary to previous reports, CDI did not adversely impact patient survival. The reasons for these differences warrant further study.

THU274

Patient social and lifestyle factors associated with cardiovascular risk affect decisions regarding transplant candidacy more than factors associated with psychological and financial well-being

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Background and Aims: Liver transplant (LT) assessment is a process to define not only if patients require transplantation, but the likely short- and long-term consequences to the candidate's health following LT. Whilst it is clear that patient co-morbidity affects LT outcomes, it is increasingly apparent that psychosocial factors influence long-term outcomes. In this study, we aim to evaluate if there are associations between psychosocial factors and outcomes of LT assessments.
Method: All LT assessments performed at King's College Hospital for UK based patients between 1/10/2018–1/10/2019 were included in this retrospective analysis. Patient demographics, liver disease aetiology and psychosocial history data were recorded from the clinical notes. Univariate and multivariate analysis were performed.
Results: 290 LT assessments were eligible for analysis. 30% of patients were declined for transplant with 17% found to have a contraindication to LT. Patients declined for LT were more likely to be: older (*58.8 v 54.0, U = 6780, p = 0.002*); Caucasian (*OR 3.78,* p = 0.004); a previous hazardous alcohol drinker (*OR 2.71*, p = 0.0002); and a current smoker

(*OR 2.14*, p = 0.04). Factors not associated with being declined for LTx were being: male (p = 0.10); currently employed (p = 0.06); a homeowner (p = 0.55); a parent (p = 0.58); and in a relationship (p = 0.76) or having a: history of substance misuse (p = 0.26); psychiatric history (p = 0.75); and history of opioid use (p = 0.63). 3 patients reported previous criminal convictions. Multiple logistic regression was performed using variables achieving significance as well as employment history and male sex (table 1). Caucasian ethnicity, age and being a current smoker were found to be associated with being declined for LT. Patients who were Caucasian were more likely to have a diagnosis of alcohol (ARLD) or non-alcohol related liver disease (NAFLD) than those who were not (*OR 2.08*, p = 0.04).

Table 1: Multiple logistic regression model of psychosocial factors influencing liver transplant candidacy

Variable	Beta	95% CI	p value
Caucasian ethnicity	1.24	1.36–10.67	0.016*
Age	0.04	1.02–1.07	0.002**
Current smoker	1.13	1.34–7.25	0.008**
Previous hazardous alcohol intake	0.55	0.98–3.07	0.06
Currently employed	−0.49	0.33–1.13	0.12
Male sex	0.38	0.81–2.64	0.21

Conclusion: Given the increased prevalence of ARLD/NAFLD amongst Caucasian patients, this would suggest that cardiovascular risk factors have a greater role in determining patients LTx candidacy than factors associated with psychological and financial wellbeing.

THU275

Inequality in access to liver transplant: are satellite liver transplant centres the answer?

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Background and Aims: It has been demonstrated that patients listed for liver transplant (LT) living further away from LT centres have worse outcomes. Although challenging to define causality, it has been hypothesised that this is due to reduced access to specialist care including LT candidacy assessment. To address this, King's College Hospital (KCH) has developed satellite LT centres (SLTC) in Northern Ireland and the Southwest and West of England. In this study, we aim to evaluate if distance from a LT centre is associated with outcomes of LT assessment and compare outcomes between KCH, SLTCs and the rest of the referral network.
Method: All LT assessments performed at KCH for UK based patients between 1/10/2018–1/10/2019 were included in this retrospective analysis. Patient demographics, clinical and laboratory data were recorded from the time of their assessment from the clinical notes. Patients referred from KCH or the non-SLTC referral network had distance and shortest driving time measured from their postcode to KCH calculated using Google maps. Patients referred from SLTCs had the same measurements calculated between patient postcode and referring SLTC. Univariate analyses were performed.
Results: 290 LT assessments were eligible for analysis. 99 patients were referred from KCH, 77 patients from SLTCs and 114 patients from the referral network. 30% of patients were declined for LT with 17% of patients having a contraindication to LT. Living greater than 60 mins drive from either KCH or a SLTC was associated with being declined for LT (*OR 1.94*, p = 0.01). There was no significant difference in risk of being declined for LT between SLTCs and KCH (p = 0.18). Patients referred from the referral network compared to KCH had a significantly higher rate of being declined for LT (OR 3.15, p = 0.0001). MELD and Child Pugh scores were significantly higher in patients referred from the referral network than KCH (*15 v 14*, *U = 2903*, p = 0.03) (*9 v 8*, *U = 2742*, p = 0.006). No significant difference was demonstrated in MELD and Child Pugh scores between SLTCs and KCH (p = 0.43) (p = 0.32).
Conclusion: Further work is required to address inequality for patients not only living further away from LT centres but those referred from non-LT centres. Developing additional SLTCs may have a role in improving access to LT.

THU276

Usefulness of phosphatidylethanol and urinary ethyl glucuronide to monitor alcohol abstinence in patients awaiting liver transplantation

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Background and Aims: Alcohol-related liver disease (ALD) is one of the most common indication for liver transplantation (LT). A period of abstinence is widely required for being registered on the waiting list, and alcohol consumption is not allowed during the waiting time. New highly specific alcohol biomarkers such as blood phosphatidylethanol (Peth) and urine ethyl glucuronide (uEtG) have been developed recently. The aim of the present preliminary study is to assess and compare on 2 consecutive periods the rates of detection of alcohol relapse during waiting time with and without the use of the new biomarkers.
Method: Medical files for all patients registered for an LT in our institution from January 2016 to November 2019 were inspected for alcohol consumption detected either by systematic blood ethanol or patient's own declaration (period 1 from January 2016 to December 2018) or using systematic uEtG and Peth (period 2 from June to November 2019). Patients were systematically asked for alcohol consumption by the medical team.
Results: During period 1, 365 patients have been registered on LT waiting list. ALD was the main etiology for 248 patients (67.9%). Alcohol consumption was detected in 12 patients (3.2%) by blood ethanol tests. Interestingly, 3 alcohol consumptions were detected as the patients were hospitalized to undergo LT. During period 2, 74 patients attended to the liver pre-transplantation unit, 52 (70.2%) of them suffering of ALD. All patients declared to be fully abstinent. Alcohol consumption was detected in 12 (16.2%) patients, cumulating 33 visits in the unit. All markers (Peth, uEtG and blood ethanol) were available for 31 of these visits. Peth was positive (>5 ng/ml) in 25/31 visits, uEtG (>500 ng/ml) in 16/31 and blood ethanol in 2/31 (both times at 0.06 g/l). Peth concentration ranged between 19 et 1135 ng/ml, reflecting consumptions between less than 14 g/day to more than 84 g/day. On 10 visits, Peth concentrations were above 326 ng/ml, potentially reflecting daily consumption of more than 50 g/day on the last 21 days. Interestingly, CDT was available in 17 of the 25 times Peth was positive (and 8 of the 10 times it was >326 ng/ml), and reflected alcohol consumption (rate >2.5%) in only 4 times, including 3/8 times when Peth detected heaving drinking.
Conclusion: Blood ethanol, medical examination and potentially CDT may be ineffective to detect alcohol consumption in patient waiting for LT, even in case of heavy drinking. New alcohol markers might represent an interesting tool to effectively monitor alcohol abstinence, and if need be, quickly provide addiction therapy to the patients who need it.

THU277

Poor dental health is a risk factor for infections by streptococci after liver transplant

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Background and Aims: Assessment of dental health in patients with cirrhosis before transplant is recommended to avoid infectious complications due hematogenous spread from dental foci after transplant. However, data to support this recommendation are scarce. We investigated liver transplant patients to clarify if dental care is necessary before transplant.
Method: Clinical, laboratory and microbiological data from patients with cirrhosis who received a liver transplant between 2010 and 2018 in our department were retrospectively analysed for oral foci of infection before transplant and infections after transplant.
Results: Data on oral health were available from 110/185 patients who received a liver transplant. Median age of patients was 53 years, 67% were male and the most frequent causes for liver transplant were alcoholic liver diseases (34%), viral hepatitis (28%) and autoimmune liver disease (14%). 35 patients showed good oral health without need for dental care, in 39 patients dental care was performed because of pretransplant assessment, 36 patients did not receive dental care despite poor oral health. The most common dental issues were caries, which affected 75% of all patients, and periodontal diseases with a prevalence of 40%. We noted that need for dental care was highest in alcoholic liver disease (95%) compared to viral hepatitis (71%) and autoimmune liver disease (73%) ($p = 0.002$). Bleeding complications due to oral care occurred in 5/13 patients, who all presented with platelets below 70 G/L and an INR above 1.5. Mortality in the first 9 months after liver transplant was similar for patients with poor oral health, after dental care and without need for dental care (19%, 11% and 14%, respectively). However, the number of infections after transplant per patient were higher in patients with poor oral health (2,9) compared to patients who had received dental care (1,9) or patients with good oral health (1,8) ($p = 0.02$). In contrast to infections by staphylococci, klebsiella or enterococci, infections by streptococci were more frequent in patients with poor oral health compared to patients without need for or after dental care (25% vs 8%; $p = 0.02$).
Conclusion: The high prevalence of dental foci of infection in liver disease patients and the increased risk for streptococci infections in patients who did not receive oral care pre-transplant suggest that assessment of oral health and oral care are important in patients awaiting liver transplant.

THU278

Pre-formed donor specific antibodies and aetiology of liver disease are associated with increased incidence of acute cellular rejections after liver transplantation

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Background and Aims: The role of donor specific HLA antibodies (DSA) in relation to clinical outcomes with liver transplantation (LT) remains debatable. This single centre UK retrospective study aimed to determine factors associated with the expression of DSA and their impact on outcomes after LT.
Method: Demographic and clinical data were collected on all consecutive adult LT recipients between January 2005 and December 2015. The detection of HLA antibodies present at the time of LT was performed using Luminex solid-phase assays and an MFI value 500 was considered positive. Multivariate logistic regression and Cox proportional hazard analysis were used to identify factors predictive of DSA expression and development of acute cellular rejection (ACR).
Results: 385 patients underwent LT and DSA data were available for 347 (90.1%). For patients with DSA data, the median age at LT was 56 years (range 17–75) and 55.6% were male. The commonest transplant indications were alcohol related liver disease (28.2%), autoimmune liver disease (AILD) (20.6%) and acute liver failure (12.8%).
Overall, 30.0% were positive for DSA with 16.1% patients having HLA class I Ab and 19% class II. Age <50 years (OR 1.93 95%CI 1.19–3.15; $P = 0.008$) and female sex (OR 2.65 95%CI 1.64–4.30; $P < 0.001$) were factors independently associated with DSA expression.
In the entire cohort, biopsy proven ACR occurred in 25.7% (99/385), of which 46.7% (43/92) had pre-formed DSAs ($p < 0.001$). This remained significant whether class I or II Ab (both $p = 0.001$). Following adjustment for age and sex, both DSA expression (OR 2.78 95%CI 1.57–4.90; $P < 0.001$) and AILD (OR 3.05 95%CI 1.52–6.10; $p = 0.002$) remained independently associated with developing ACR. Patients who express DSA were more likely to develop ACR within 6 months (Hazard Ratio 2.31 95% CI 1.47–3.64; $p < 0.001$, Figure 1). There was no significant association between the presence of pre-formed DSA and the development of biliary strictures ($p = 0.246$) or all-cause mortality ($p = 0.871$).

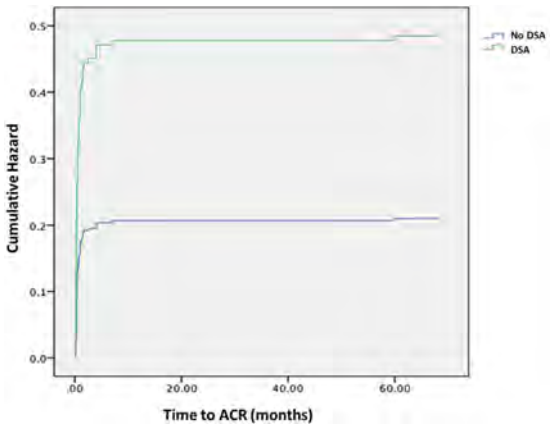

Figure: Cox Regression Curve (adjusted for age<50, sex and aetiology) for time to development of ACR

Conclusion: DSA are more frequent in patients who are female or under 50 years old. DSA expression is associated with an increased risk of developing ACR but is not predictive of overall patient survival. Further work is needed to examine the role of de novo DSA in the development of post-transplant complications.

THU279

Sustained virological response with DAAs decreases glucose level but do not improve renal function, lipid metabolism and blood pressure in liver transplanted patients: a 3-year, long-term follow up

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Background and Aims: DAAs allowed reduction of HCV-related liver graft failure. Improvement in metabolic profile was reported during a short 48 weeks observation period after SVR. To evaluate, in LT patients (Pts), the impact of SVR on metabolism, renal and liver function and on arterial hypertension during 3 years of follow up (FU).
Method: Assessment of metabolic, kidney and liver function changes, as well as antihypertensive drug modifications, were collected up to 3 years of FU after completion of DAAs therapy. Mean differences were calculated with Anova test and linear regression for continues variables and Fisher' exact test for categorized variable.
Results: 152 LT Pts; all but 6 (n = 152, 96%) showed SVR. Pts : males 84%; age: median 63 yrs (IQR 57–70); baseline MELD 9, (IQR 7–12); cirrhosis 26%; HCC diagnosis 36%; SVR was associated with a decrease in fasting glucose in pts without overt diabetes, with a statistical significance at 3 yr vs. baseline −5.5 mg/dl ±22 ($p < 0.004$). In diabetic pts, mean fasting glucose level showed a trend to decline. Dyslipidemia prevalence increased over time, with a 12.6% incidence (33.3% at 3 yr vs. 20.7% at baseline), as well as BMI (+2.6 at 3 yr ±9; $p = 0.003$). An improvement in liver function was recorded at 1 yr and 3 yr as expressed by bilirubin decrease (mean −0.12 mg/dl ±0.7 [$p < 0.05$] and −0.78 mg/dl ±1.0, respectively [$p < 0.001$]) and albumin increased concentrations (+0.14 g/l at 3 yr. ±0.5; $p = 0.01$). MELD score decreased over time −1.26 at 3 yr; $p < 0.001$). As expected the through serum level of immunosuppressive drugs declined over time ($p < 0.0001$ at 3 yr) showing strong correlation ($p < 0.001$) with creatinine level, and borderline ($p = 0.056$) with glucose level. Moreover, creatinine showed a significant mean increase after SVR (1 yr vs. baseline 0.06 mg/dl ±0.2; 3 yr vs. baseline 0.08 mg/dl ±0.3 ($p < 0.001$). Kidney function deteriorated over time with 34.5% of Pts on CKD ≤3 at 3 yr vs. 24.8% at baseline ($p < 0.001$). Incidence of arterial hypertension was 4.0% at 1 yr and 8.5% at 3 yr compared to baseline ($p < 0.001$), potential expression of the long interval between LT and DAAs therapy (mean 73 months, IQR 22–131) and of preexisting renal and vascular involvement.
Conclusion: elimination of HCV in LT could have a beneficial impact on glucose metabolism but does not improve lipid profile or reno-vascular complications, which are possibly associated to the long-term exposure to immunosuppressive drugs.

THU280
Prospective multicenter study of sofosbuvir-velpatasvir (SOF/VEL) in hepatitis C virus (HCV) negative liver (LT) and kidney transplant (KT) recipients receiving HCV viremic donors

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Background and Aims: A greater pool of HCV-viremic donors has led to expanded use of these organs in transplant recipients without HCV infection with the goal of reducing wait-list morbidity and mortality. The optimal treatment strategy is unclear, in terms of best DAA option, timing of initiation and duration of therapy. We sought to evaluate the safety and efficacy of SOF/VEL for 12 weeks among HCV-negative LT and KT recipients.
Method: 6 U.S. transplant programs prospectively enrolled adults listed for primary LT or KT with the following exclusions: re-transplant, HBV or HIV infection, multiorgan (except SLK). Donor exclusions were >F1 for LT and kidney donor profile index >85% for KT. SOF/VEL was started once viremia was confirmed post-transplant and patient judged to be clinically stable. The primary endpoints were SVR12 and safety.
Results: Of 115 patients consented, 23 were transplanted (12 liver, 11 kidney) of whom 22 became viremic post-transplant. Recipients had mean age 54 yrs, 57% male; donors' mean was 38 years, 78% male, with 74% with confirmed brain death. HCV genotypes were 57% GT1, 26%GT2, 4%GT3 and remainder not determined. Median log HCV RNA on day 3 was 6.45 (range 1.2–8) in LT and 3.59 (range 1.3–4.7) in KT; the kinetics of HCV RNA decline are shown in Table. All reaching the SVR12 timepoint are HCV negative (13/13), including 2 with detectable HCV RNA at end of treatment. Serious adverse events considered to be possibly related include: 1 antibody-mediated rejection (in A2 to O LT recipient) and 1 progressive biliary sclerosis of indeterminant etiology after LT. Delays in treatment initiation (n = 5 beyond day 21) were related to delayed renal recovery (n = 3), administration of amiodarone (n = 1) and provider preference (n = 1).
Conclusion: SOF/VEL for 12 weeks was highly effective therapy for HCV-negative liver and kidney transplant recipients who received HCV-viremic donors. All transmitted infections (22/23) were detectable by day 3, with different viral kinetics in KT versus LT, supporting early initiation of antiviral therapy. Safety was excellent but vigilance of immune-mediated complications is warranted.

THU281
Incidence and prognostic impact of cancer after liver transplantation

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	Liver Recipients (N=12)	Kidney Recipients (N=11)
Days from transplant and Start SOF/VEL, median, range	7 (4-25)	16 (5-28)
Post-op Day 3 HCV RNA, median, range (log)	6.45 (1.18-8.0)	3.59 (1.28-4.65)*
Tx Start HCV RNA, median, range (log)	5.81 (4.8-7.19)	6.6 (2.69-7.56)*
Day 7 Tx HCV RNA, median, range (log)	1.82 (1.18-3.0)	3.36 (1-5.09)*
Day 7 Quantifiable/TNQ/TND (N)	10/2/0	6/1/1
Week 4 Tx HCV RNA, median, range (log)	1.00	1.60
Week 4 Quantifiable/TNQ/TND (N)	0/1/10	4/1/2
EOT Quantifiable/ TNQ/TND. (N)	0/0/10	0/2/5
SVR12 (N)	7/7	6/6

TNQ= target detected but no quantifiable; TND target not detected
* Viremic patients only (1 KT patient was aviremic post-transplant)

Figure: (abstract: THU280)

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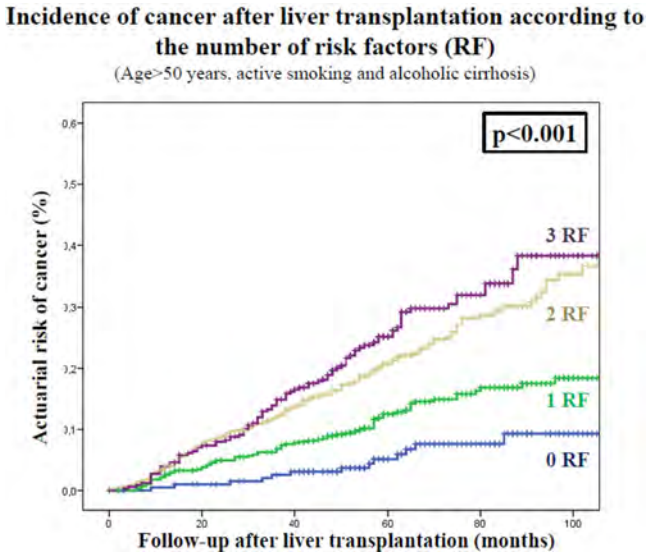
Background and Aims: Cancer screening protocols after liver transplantation (LT) are lacking. We aimed to determine the incidence of cancer after LT and its clinical risk factors.
Method: Observational multicenter study including a consecutive cohort of patients who underwent LT (2010–1015) in 10 Spanish institutions, survived longer than 1 year and received tacrolimus-based immunosuppression. Exclusion criteria: Age<18, combined organ transplantation, retransplantation and HIV+. The incidence of cancer and related mortality were evaluated by using Cox's regression. Standardized incidence rate (SIR) was calculated with general population data obtained from Globocan 2018 (available at https://gco.iarc.fr/).



Results: A total of 1,732 patients were included: mean age 54.4 ± 9.6, 76.3% males, 49% alcoholic cirrhosis, 37.4% with hepatitis C. The indication for LT was hepatocellular carcinoma in 703 patients (40.6%). Median follow-up after LT was 64 months (IQR 48–86). Three hundred and thirty-two patients developed cancer: cumulative incidence = 17% at 5 years; incidence rate = 0.038 cases/person*years; SIR = 3.19 (excluding hepatocellular carcinoma). The incidence of cancer remained unchanged during the inclusion period. The onset of cancer impacted negatively on post-LT survival: 64.1% vs 91.3% at 5 years. Letality of cancer was 46.4%, with a median life expectancy of 6 months (IQR 2–15). After controlling for baseline hepatocellular carcinoma, the independent risk factors of cancer were: Age>50 years old (RR = 2.49; p < 0.001), active smoking (RR = 1.44; p = 0.002) and alcoholic cirrhosis (RR = 1.42; p = 0.003). The number of risk factors was associated with a progressive increase of cancer rates at 5 years: 5.1% in absence of risk factors, 12.5% with 1 risk factor, 20.7% with 2 risk factors and 25.1% with 3 risk factors (figure).
Conclusion: The incidence of cancer after LT is high and carries a dismal prognosis. A consensus is needed to delineate cancer screening strategies after LT, which should be tailored according to the history of smoking and alcoholism.

THU282

Gender disparity in cardiovascular morbidity and mortality post liver transplantation

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Background and Aims: Understanding factors associated with long-term survival after liver transplant (LT) is important for predicting, and potentially improving outcomes. Several factors have been implicated in reduced long term survival including older age, frailty, cardiovascular morbidities, and psychosocial factors. Women constitute a unique group of patients defined not only by body mass index (BMI), different etiologies of disease, and psychosocial factors but also by hormonal factors. The interplay of these factors may alter disease course and ultimately transplant outcomes. In this study, we examined the cardiovascular event risk of all liver transplant recipients by gender.
Method: All patients who had LT from January 2007 to January 2017 were evaluated (N = 496). Protocol coronary angiography was performed in all patients ages>50 years, history of coronary artery disease (CAD), abnormal cardiac stress test or risk factors for CAD. A cardiovascular composite outcome including acute coronary syndrome, symptomatic arrhythmia, cardiac arrest, stroke, or cardiac death occurring post LT was the primary outcome. Secondary endpoints included cardiovascular mortality and all-cause mortality.
Results: Our study population was comprised of 137 (27.6%) females. Most common causes of liver disease were alcohol (15.7%), chronic hepatitis C (45.8%), and nonalcoholic steatohepatitis (15.9%). Pre-transplant evaluation for CAD found that there was no statistically significant difference in CAD between males and females (28% vs. 20%, p = 0.1). There was no difference in prevalence of hypertension, hyperlipidemia and diabetes between genders in our study group. In the post-transplant period, men had higher incidence of cardiovascular events (primary outcome), (23.1% vs. 12.4% p = 0.006). The majority of events consisted of symptomatic arrythmia, the incidence of which was higher in men (17.5% vs. 9.5%, p = .02). While the overall incidence of cardiac-related death was 6.7% during the study period, this was significantly higher in men compared to women (8.1% vs 2.9%, p = 0.04). However, there was no difference in all-cause mortality between genders.
Conclusion: In this study of liver transplant recipients, we found that males had a higher risk of cardiovascular events and cardiac death, while the prevalence of cardiovascular risk factors was similar between genders.

THU283

GFR reset point at 3 months after liver transplant is a superior predictor of liver and kidney disease related outcomes: analysis from a large cohort of NASH patients (nail NASH consortium)

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Background and Aims: Since the introduction of the MELD score increasing number of patients with renal failure is being transplanted. The evolution of renal function based on the on severity of renal dysfunction at the time of LT is unclear in patients with NASH. We examined, (1) the association of pretransplant renal dysfunction (eGFR closet to LT) with the slope of renal function after LT, (2) incident CKD events after LT, (3) time to progression to CKD after LT and (3) all-cause mortality after LT.

Method: From the NailNASH consortium data set, we identified 696 NASH recipients who received deceased donor LT. Recipients were analyzed in 3 groups: Low GFR (LGFR) (estimated glomerular filtration rate (eGFR) <30 mL/minute/1.73 m^2 at LT; n = 108); High GFR (HGFR) (eGFR ≥ 30 mL/minute/1.73 m^2; n = 483); and those with SLKT (n = 105). The longitudinal data set with eGFR at transplant (0) and 3, 6, 12, 24, 36, 48, and 60 months post-LT. CKD was defined as two eGFR levels <30 mL/min/1.73 m^2 separated by ≥90 days.

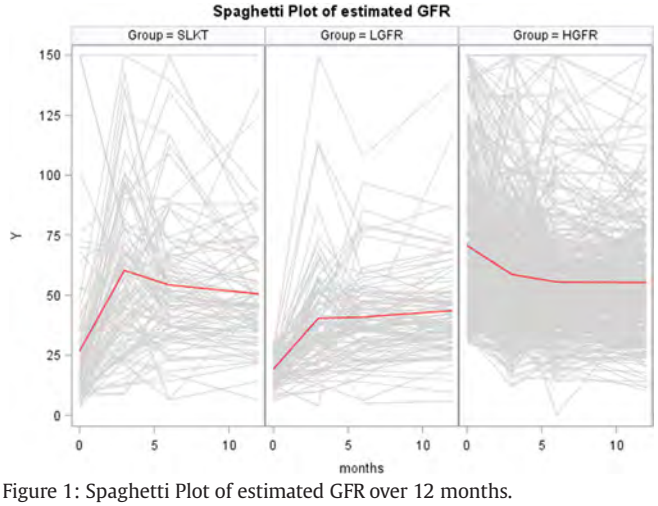

Figure 1: Spaghetti Plot of estimated GFR over 12 months.

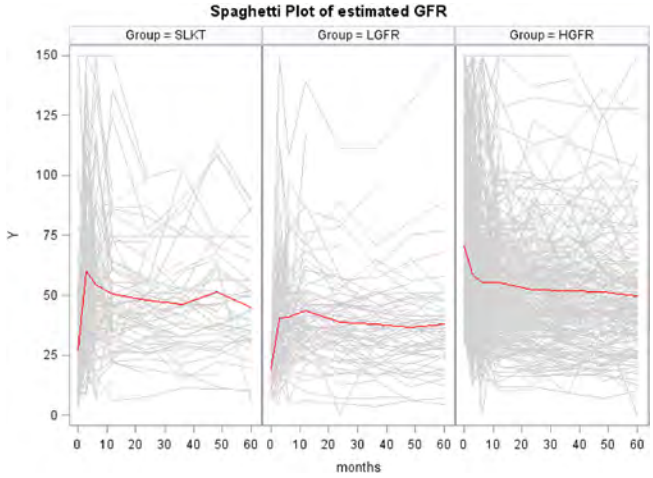

Figure 2: Spaghetti Plot of estimated GFR over 60 months.

Results: Mean age at LT was 60 ± 9 years, 49% male, 74% Caucasian. We censored follow up at 5 years. Figure 1 and 2 represents the eGFR over time by group (over 12 months, and over 60 months respectively) with mean eGFR over time (red line). A statistically significant change in the slope for eGFR at 3 months after LT was noted in all three groups, called as "GFR reset point." The difference between the eGFR slope before 3 months and after 3 months estimated by linear mixed-effects model was significant in all 3 groups (p < 0.0001). Overall unadjusted incident CKD rate was 21.3/1000 patient-years (95%CI: 16.7–25.9). The unadjusted incident CKD rate was significantly higher among patients in the LGFR group (crude incident CKD rate: 48.1/1000 patient-years (95%CI: 32.0–64.3) compared to patients with HGFR (crude incident CKD rate: 15.7/1000 patient-years (95% CI: 10.9–20.5; p < 0.0001) after Bonferroni correction for multiple testing, but not significantly different compared to SLKT group (crude incident CKD rate: 19.1/1000 patient-years (95%CI: 7.–30.3; p = 0.57). Time to CKD event analysis using Kaplan-Meier curves showed a significantly increased risk of progression to CKD in the LGFR group using either preLT GFR (p < 0.0001) or the 3-month post LT reset point (p = 0.05) as the baseline. Additionally, LGFR group had worse overall patient survival using the 3 month "reset point" point as the baseline (P < 0.0001).

Conclusion: In a large multicenter cohort of LT recipients with NASH, grouped by severity of renal dysfunction at the preLT period, a statistically significant change in the slope for eGFR at 3 months after LT (GFR reset point) was noted. Long term liver and kidney disease outcome appears to be modified by this new baseline. LGFR group had increased risk for progression to CKD as well as overall mortality.

THU284

Is hepatitis B immunoglobulin necessary for hepatitis D prophylaxis after liver transplantation? A retrospective multicenter study of a cohort of 174 patients

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Background and Aims: Chronic hepatitis caused by hepatitis delta virus (HDV) is the most severe form of viral hepatitis, with rapid progression to cirrhosis, which may lead to liver transplantation (LT). It is generally accepted that post-LT prophylaxis includes a nucleos(t)ide analog (NUC) and anti-hepatitis B immunoglobulin (HBIG), which would prevent HDV reactivation in case of surface antigen (HBsAg) reappearance. Our aim was to describe HDV/HBV prophylaxis in real clinical practice in LT recipients and to analyse the incidence and impact of HDV recurrence.
Method: Retrospective study in 10 Spanish Liver Transplant centers. Relevant variables within the pre-LT, LT and post-LT periods were collected from all patients transplanted due to HBV/HDV coinfection between 1988 and 2018.
Results: Of a total of 987 patients undergoing LT due to HBV, 174 (17%) had HDV coinfection. 75% were men, median age at LT 45 years (36–52), 77% were Spanish and 15% from Eastern Europe. The indications for LT were decompensated cirrhosis (68%), decompensated cirrhosis and hepatocellular carcinoma (HCC) (19%), HCC (9%) or fulminant hepatitis (4%). Median MELD score was 18 (15–22) and median Child-Pugh 10 (9–11). At time of LT all patients were HBsAg positive, 17% had detectable HBV-DNA and 55% were on treatment with NUCs. HDV-RNA was available in 76 (44%) and 84% were positive; only 12% had received treatment for HDV. HCV or HIV coinfections were present in 11% and 8% of cases, respectively.
The median post-LT follow-up was 7.8 (2.3–15.1) years. 97% received HBIG in the immediate post-LT, but only 42% were currently on HBIG. The median time that patients were on HBIG was 18 (7–52) months. Reasons for HBIG discontinuation were patient dropout (11%) or center's protocol (66%). At time of analysis 90% were on NUCs and 10% were not receiving any prophylaxis.
During post-LT follow-up, HBsAg was detected in 19 (11%) patients, 48% within the first year and 21% within the second; 6 (32%) were still on HBIG, but only 2 (10%) had anti-HBs >10 U/ml. Regarding NUCs prophylaxis 9 patients were on lamivudine, one on tenofovir and 9 did not receive NUCs. HBV-DNA was detected in 11 (7%) patients, 9 coinciding with reappearance of HBsAg and in 7 (63%) associated with an increase in transaminases. HDV-RNA was detected in only 2 patients; one died due to decompensated cirrhosis. Patients' survival at 1, 5 and 10 years after LT was 95%, 90% and 88%, respectively.
Conclusion: Despite the recommendation of long-term HBIG prophylaxis in HBV/HDV LT recipients, only a minority of patients were on HBIG 2 years after transplantation. Nevertheless, cases of HDV reactivation were rare, even in case of HBsAg reappearance. Despite the limitations of the study, our data do not support the use of long-term HBIG prophylaxis in HBV/HDV LT.

THU285

Pre-transplant diabetes independently predicts atherosclerotic vascular event and death due to cardiovascular disease in liver transplant recipients: a long term multicenter observational study

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Background and Aims: Liver transplant (LT) recipients often develop metabolic disorders and cardiovascular disease that definitely represent main driver of both morbidity and mortality. Aims of the present study were to detect predictors of atherosclerotic vascular event (AVE), and to assess the impact of AVE on the long-term outcome.
Method: We retrospectively analyzed data from patients transplanted between 2000 and 2005 and followed-up in five Italian *Transplant Outpatient Clinics*. Cox Regression analysis was performed for predictors of AVE, global mortality, and cardiovascular mortality. Survival analysis was completed using the Kaplan-Meier method. $P < 0.05$ was considered significant for all tests.
Results: We analyzed data from 367 subjects registering 37 post-LT AVE during a median follow-up of 14 years. Patients with AVE more frequently showed pre-diabetes mellitus (DM) in respect to the others (48.6 vs 13.9%, $p = 0.000$). In the post-LT period, patients with AVE satisfied criteria of metabolic syndrome in 83.8% of cases while subjects without AVE in 36.7% ($p = 0.000$). At Multivariate analysis pre-LT DM independently correlated with AVE (HR 2.250, CI 10.440–4.848, $p = 0.038$). Moreover, pre-LT DM and AVE were strongly associated with heart-related death (HR 5.418, CI 1.060–29.183, $p = 0.049$ and HR 86.097, CI 9.510–779.480, $p = 0.000$, respectively).
Conclusion: Pre-LT DM is a main risk factor for post-LT AVE and both pre-LT DM and post-LT AVE are strong long-term predictors of heart-related death. Patients with pre-LT DM should obtain a personalized follow-up for prevention or early diagnosis of AVE.

THU286

A novel scoring system for predicting risk of relapse following referral for liver transplantation in patients with alcohol-related liver disease

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Background and Aims: Liver transplantation (LT) is an established treatment for the management of decompensated cirrhosis and hepatocellular carcinoma. Approximately 15% of adult LT in Australia and New Zealand are performed for alcohol-related liver disease (ALD). Alcohol relapse, defined as any alcohol after LT, is reported in 20–50% of patients. Risk of relapse to alcohol after referral for LT, including whilst on the waiting list, is not well documented. The aim of this study was to develop a prognostic score from pre-LT variables to predict the relapse risk in patients with ALD referred for LT.
Method: This retrospective observational study conducted at a single LT centre included all patients referred for LT with ALD as a primary or secondary diagnosis between January 2013 and August 2019. Alcohol relapse was defined as positive blood alcohol level (BAL) or any self-reported intake of alcohol. Harmful relapse was defined as alcohol

consumption associated with medical or social harm including positive BAL on the LT waiting list. Binomial logistic regression was used to identify several pre LT patient variables associated with alcohol relapse after LT. These variables were used to construct a prognostic score to predict risk of relapse. The scoring system was analysed using the area under the receiver operating characteristic curve. All statistics were performed using SPSS.

Results: Of 712 adult patients were referred for LT during the study period and 150 (21%) had ALD. Of those, 127 (84.7%) were male with a mean age at time of referral of 54 years and median duration of abstinence pre-referral of 14.5 months (range, 0.67–416). 14 (9.3%) patients were delisted prior to LT due to positive BAL. 13 (8.7%) relapsed post-LT including 5 (3.3%) patients with harmful relapse. On multivariate analysis, four variables were associated with alcohol relapse: LT indication for decompensated ALD [OR 5.48 (95% CI 1.79–16.77), p = 0.022], relapse despite prior specialist advice [OR 3.10 (95% CI 1.22–7.86), p = 0.035], time since diagnosis of ALD [OR 0.859 (95% CI 0.74–1.00), p = 0.044] and documented concern of relapse by transplant hepatologist [OR 4.44 (95% CI 1.85–10.68), p = 0.049]. The Alcohol Risk Assessment Score (ARAS) was developed using these variables (Table 1). Documented concern from transplant hepatologist was excluded from the model due to concerns regarding subjectivity. On modelling, the ARAS produced an AUROC of 0.76 (95% CI 0.66–0.85) for accurately predicting alcohol relapse post-LT. An ARAS score >3 gave NPV 92.5%, PPV 26.5%, sensitivity 81.5% and specificity 50.4% for predicting alcohol relapse after LT referral.

Table 1. Alcohol Risk Assessment Score

Variable	*Points*
Indication for LT	
Decompensated ALD	3
HCC	0
Prior relapse despite specialist advice	2
ALD diagnosed <4 years ago	1

Conclusion: This novel scoring system is a useful predictor of alcohol relapse in patients with ALD referred for LT. It may assist LT committees in identifying patients at high risk of relapse and guiding clinicians in introducing early risk-based interventions before and after LT.

THU287

Improvement of renal function prior to liver transplantation is not associated with better long-term renal outcome or mortality

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Background and Aims: Since the MELD score (model for end stage liver disease) has been introduced in the liver allograft allocation system renal impairment in liver transplant (LT) recipients has become a topic of increasing importance. This is the first study evaluating the course of renal function prior to LT as a risk factor for long-term renal outcome and overall survival.

Method: All adult patients undergoing LT at the University Medical Centre Hamburg-Eppendorf between 2011 and 2015 were included in this retrospective study. Renal function over a period of 3 months prior to LT as well as long-term renal outcome and survival was assessed in all patients.

Results: Altogether 226 patients with a median age of 60 years (female: 37%) were included in this study. Median follow up post LT was 1491 days. Patients were classified according to the nadir GFR value within a period of 3 months prior to LT (CKD 1: n = 30 (13%), CKD 2: n = 64 (28%), CKD 3: n = 42 (19%), CKD 4: n = 42 (19%) and CKD 5: n = 48 (21%)). With respect to the GFR at the day of LT renal function improved (one CKD stage) in 63 patients (28%) whereas it remained stable or deteriorated in 163 patients (72%). However, course of renal function prior to LT did neither significantly affect 3-moth survival (p = 0.9), 1-year survival (p = 0.6) nor 5-year patients' survival (p = 0.4), as illustrated in figure 1. Furthermore, CKD stage at end of follow-up did not significantly differ between patients with and without improvement of kidney function prior to LT (p = 0.8). Nevertheless, both, need for dialysis pre LT was associated with increased 5-year mortality (56% vs. 29%, p < 0.05) as well as need for dialysis post LT (58% vs. 14%, p < 0.05).

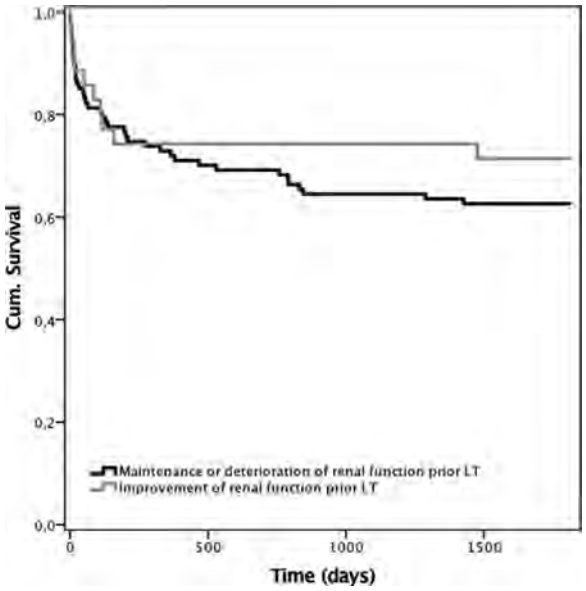

Figure: Kaplan Meier plot of 5-year survival according to alterations (improvement vs. maintenance or deterioration) of renal function (within a time period of 3 months) prior to LT; Log-rank test: p = 0.4

Conclusion: Dialysis pre and postoperatively affected survival in this long-term follow up observational study. However, improvement or worsening of renal function immediately prior to LT had no significant effect on long-term renal or overall outcome. As alterations of renal function and subsequent changes of the MELD score directly affect prioritization of organ allocation, future studies need to clarify the impact of alterations of serum creatinine on waiting time in patients prior to LT.

THU288

An open-label, cohort study of grazoprevir/elbasvir combination therapy for patients with genotype 1b chronic hepatitis C after liver or kidney transplantation

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Background and Aims: Although some new direct-acting antivirals (DAAs) have been used for organ transplantation recipients, individual limitations, such as drug-drug interaction (DDI), may

limit their clinical use. Grazoprevir (GZR)/elbasvir (EBR) is highly effective in the treatment of genotype 1b chronic hepatitis C, but its clinical data on the treatment for patients after liver or kidney transplantation remain lacking. The aim of this study is to assess the efficacy and tolerability of GZR/EBR combination therapy in genotype 1b HCV-infected liver or kidney transplant recipients.

Method: In this phase 4, multi-center, open-label, interventional, single-arm cohort study (ClinicalTrials.gov number NCT03723824), patients receive GZR/EBR for 12 weeks. Inclusion criteria: (1) Chronically infected with genotypes 1b HCV; (2) Underwent liver and/or kidney transplantation; (3) Without clinical or pathologic evidence of moderate or severe rejection. Exclusion criteria: (1) HCV genotype other than 1b; (2) Liver decompensation; (3) Co-infected with HIV or HBV; (4) Prior exposure to an NS5a inhibitor; (5) Any active malignancies; (6) Hemoglobin level less than 10 g/dL; (7) Platelet level of 75,000/mm^3 or less; (8) ALT, AST, or ALKP greater than 10X upper limit of normal (ULN) or more; (9) Total bilirubin greater than 3X ULN or more; (10) Albumin less than 3 g/dL; (11) Using medication that is not considered safe to co-administer with GZR/EBR, such as cyclosporine. The primary endpoints are SVR12 and discontinuations due to adverse events (AEs).

Results: Until the end of October, 2019, 11 patients were enrolled into this study, including 8 (72.7%) kidney and 3 (27.3%) liver transplant recipients. The median age was 66.0 (62.0–69.0) years, and 4 (36.3%) patients were males. The median duration was 10.4 (0.13–15.9) years from the date of organ transplant. The most commonly used immunosuppressants were tacrolimus (100%), everolimus (36.3%), and mycophenolate mofetil (45.5%). The median HCV viral load was 6.30 (5.53–6.93) log^{10} IU/mL at baseline. No patient had liver cirrhosis, and 1 patient (9.1%) was interferon-experienced. In patients whose antiviral responses could be accessed, the rates of RVR, EOT, and SVR12 were 100% (8/8), 100% (7/7), and 100% (4/4), respectively. No patient needed to adjust the dosage of immunosuppressants. No AE was deemed by the investigators to be GZR/EBR-related, and no patient discontinued GZR/EBR during the GZR/EBR therapy period. No transplant organ rejection episodes or deaths occurred during the study period.

Conclusion: In this interim analysis, GZR/EBR is highly effective and well tolerated in genotype 1b HCV-infected liver or kidney transplant recipients, and its DDIs are generally easy to be managed.

THU289

Proximal splenorenal shunt as a secondary prophylaxis for isolated gastric bleeding in patients with non-cirrhotic portal hypertension: a report from a single-center case-series

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Background and Aims: Gastric variceal bleeding is a frequent problem in patients with non-cirrhotic portal hypertension (NCPH), and endoscopic glue therapy is currently the treatment of choice. However, glue therapy often requires multiple sessions, is associated with risk of thrombo-embolic complications, and not immediately available to patients residing in the rural and remote areas. Because variceal bleeding rather than liver failure is the common cause of death in such patients, we performed splenectomy and proximal splenorenal shunt (PSRS) in NCPH patients with history of gastric variceal bleeding as secondary prophylaxis, and here presents our experience.

Method: This study was conducted at Indira Gandhi Institute of Medical Sciences, Patna, India between January 2012 and June 2017. During this period, 55 patients with NCPH and gastric variceal bleeding presented to us. Patients with suspicion of underlying cirrhosis (n = 04), associated oesophageal varices (n = 18), unsuitable splenic vein for shunt surgery (n = 6) and those unwilling to undergo surgical procedure (n = 02) were excluded from study. PSRS was performed in 25 NCPH patients which included extrahepatic portal vein obstruction (EHPVO, n = 19) and non-cirrhotic portal fibrosis (NCPF, n = 06). Patients were followed up every three months for one year, every 6 months for the second, and yearly thereafter by telephonic conversation and outdoor visits. All patients underwent Upper GI Endoscopy and Doppler Ultrasonography 6 months after surgery to see the status of varices and shunt patency.

Results: The mean age NCPH patients was 18.6 ± 3 years and the majority were male (76%). The median episodes of bleeding prior to surgery was 02 (01–06). An end-to-side PSRS was done in all with a mean shunt diameter of 8.4 mm. The average operative time was 4.5 ± 0.5 hours and the average blood loss during the operation was 865 ± 315 ml. Twenty patients (80%) were followed up for a median period of 3.4 (01–06) years. Gastric Variceal regression was noted in all 20 patients with disappearance of gastric varices in 08 patients. Shunt thrombosis was noted in 20% patients and two of such patients developed rebleeding 6 months and 3 years after shunt surgery, respectively. Features of hypersplenism improved in all patients.

Conclusion: Considering limitations of glue therapy, PSRS is one time, safe and effective therapy in patients with EHPVO and NCPF patients. However, a study using larger sample and control arm is needed.

THU290

Usefulness of the "AFP model" to predict recurrence tumor in patients transplanted with carcinoma hepatocellular within Milan criteria

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Background and Aims: In patients with hepatocellular carcinoma (HCC), elevated AFP levels is a predictor of poor prognosis, both transplanted and non-transplanted. Levels >1000 ng/ml have been associated with high risk of tumor recurrence (TR) post-transplant. In the last years, they have developed prognostic TR models that incorporate AFP, and appear to improve TR prediction post-transplant compared to the Milan criteria. The aims of this study was to evaluate the usefulness of the "AFP Model" to predict TR in patients transplanted with HCC within Milan criteria pre-transplant.

Method: 195 patients transplanted consecutively with HCC within Milan criteria pre-transplant were included. The median follow-up was 4.6 years. The patients with survival less than 3 months postoperatively were excluded. The 87% were men with a median age of 58 years (43–67). The etiology of the hepatic disease was alcohol (45%), HCV (42%), HBV (5%) and others (8%). Variables analyzed: baseline AFP, number and size of tumor nodules pre-transplant and in the explant, tumor differentiation, vascular invasion and scoring of the "AFP Model."

Results: The TR rate was 9.7% (19/195). The 94% of the patients had a score of the "AFP Model" ≤2 (137 patients with score 0; 32 with score 1; 15 with score 2; 10 with score 3 and 1 patient with score 4). The 26% (5/19) of the TR were developed in patients with a score >2 and they represented 5.6% (11/195) of all the cohort. Of those with a score >2, the 45% (5/11) presented TR, compared with 7.6% (14/184) of those with a score ≤2 (p = 0.001). The explant presented criteria >Milan in 63% (7/11) of patients with score >2 and in 16% (31/184) with score ≤2 (p = 0.002). Microvascular invasion was observed in 36% (4/11) of the explants with score >2 and in 10% (19/184) with score ≤2 (p = 0.02). The waitlist time was significantly lower in patients with a score >2 (41.5 ± 36.3 vs 89 ± 82.8 days; p = 0.001). The probability of TR post-transplant at 1,3 and 5 years was higher in patients with a score >2 (10%, 42% and 57% vs 1.7%, 6.7% and 9.6%; p < 0.001). TR-free survival at 1.3 and 5 years was greater in patients with

score ≤2 (96%, 87% and 77% vs 90%, 57% and 43%; p = 0.005) as well as overall survival (98%, 91% and 82% vs 91%, 60% and 60%; p = 0.02).
Conclusion: In patients transplanted by HCC within Milan criteria pre-transplant, the "AFP Model" was able to differentiate 2 groups with a different probability of post-transplant tumor recurrence and with different survival, which confirms its usefulness in the selection of patients for transplant. In our patient series, the application of the "AFP Model" would have avoided a quarter of the tumor recurrences excluding from the transplant only a small number of patients.

THU291

Therapy with DAA increases post-OLT survival but not the risk of recurrence in patients undergoing liver transplantation for HCV-related HCC

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Background and Aims: The role of direct acting antivirals (DAA) for hepatitis C virus (HCV) in hepatocellular carcinoma (HCC) recurrence is a source of great debate. Current evidence is not able to determine whether DAA therapy either increases or decreases risk of recurrence. However, it has not been thoroughly investigated the role of DAA therapy in patients undergoing orthotopic liver transplantation (OLT) for HCC. As a post-OLT recurrence is an almost invariably deadly event, we aimed to compare the risk of recurrence and the overall survival (OS) of patients treated with DAA and obtaining sustained virological response (SVR) before OLT with an historical cohort of patients transplanted for HCC before the arrival of DAAs.
Method: We enrolled retrospectively 48 patients from the Bologna Liver Transplant Unit who underwent OLT in the DAA era for HCV-related HCC, from 2015 to 2019, comparing to an historic cohort of 128 patients that were transplanted for the same indication from 2003 to 2013. We performed multivariable regression analysis to identify factors associated with time to recurrence and overall survival.
Results: Recurrence rate was 12.5% for the first group (mean time to recurrence 16.8 mo) and 20.3% for the second (mean time to recurrence 24.5 mo). OS was significantly different: 91.7% vs 60.6%. In the Cox analysis, active HCC at transplant, number of nodules and diameter of the largest nodule and alpha-fetoprotein were significantly associated with time-to-progression, whilst OS was associated with DAA treatment, microvascular invasion, diameter of the largest nodule at transplant and LN_{10}AFP at transplant. Analysing the competing causes of death, most of the effects on the increased survival in the DAA cohort derived for the reduction of the risk of liver decompensation.
Conclusion: Post-OLT recurrence did not vary significantly between the two groups. However, overall survival is increased in the DAA group. Therefore probably their efficacy is due to other effects, in particular the prevention of liver decompensation.

THU292

Geographic disparities and socioeconomic determinants in liver transplantation referral at the Scottish Liver Transplant Unit

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Background and Aims: Previous studies have shown geographical and socioeconomic disparities in patients' access to liver transplantation. The aim of the study is to assess whether distance from transplant centre and socioeconomic status are associated with worsened outcome.
Method: We performed a retrospective study at Scottish Liver Transplant Unit (SLTU) looking at all transplant assessments for alcohol-related liver disease (ARLD), hepatocellular carcinoma (HCC) and non-alcoholic fatty liver disease (NAFLD) from 1/1/2007 to 31/12/2017. Patients' demographics including gender, age, referring health boards, Scottish Index of Multiple Deprivation (SIMD) decile and distance from SLTU were recorded. Patients' clinical characteristics including UKELD (United Kingdom Model for End-Stage Liver Disease) scores and aetiology of their liver disease were also included. The outcomes of the study included transplant listing outcome and mortality after liver transplantation.
Results: 937 patients (median age 59, IQR 52–64, Male: 75%) with a diagnosis of ARLD (n = 667), NAFLD (n = 157) and/or HCC (n = 432) were admitted for transplant assessments during the 11 years study period. 479/937 (51%) patients were listed for transplant, 403/479 (84%) patients received liver transplantation and of these 68 (17%) died. Multivariable logistic analysis showed the odds of being listed for transplant were 9% higher with each increasing SIMD decile (OR 1.09, CI 1.04–1.14, p value <0.001). Other statistically significant variables associated with transplant listing included the diagnosis of HCC (OR 1.80, CI 1.19–2.73, p value = 0.005) and UKELD score (OR 1.03, CI 1.00–1.06, p value = 0.03). The mortality rate after liver transplant decreased with each increasing SIMD decile but it was not statistically significant (OR 0.92, CI 0.83–1.01, p value = 0.09). Geographic distance from SLTU had no statistically significant association with transplant listing outcome or mortality outcome after transplant.
Conclusion: Our study demonstrated no geographical disparity in referral and assessment at SLTU. However, patients from a more deprived area (SIMD decile 1) were less likely to be listed for transplant. Future prospective studies are required to investigate the causation of these correlations.

THU293

Pre-operative biliary drainage in perihilar cholangiocarcinoma: an overview of systematic reviews

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Background and Aims: The beneficial effect and route of preoperative biliary drainage (PBD) which can be via percutaneous transhepatic biliary drainage (PTBD) or endoscopic biliary drainage (EBD) in patients with perihilar cholangiocarcinoma (pCCA) are heavily debated. An overview of systematic reviews allows assessment of quality of individual systematic reviews. We performed an overview of systematic reviews to comprehensively collate evidences and clarify the effect of PBD on drainage-related and postoperative outcomes in patients with resectable pCCA to provide the best possible evidence-based recommendations.
Method: An overview of systematic reviews was prospectively registered in PROSPERO (CRD42019141412). A systematic search was performed in PubMed, Embase, Cochrane Library and KSR Evidence from inception to May 31, 2019. We included studies that assessed the use of PBD, and/or compared PTBD and EBD in patients with resectable pCCA. The primary outcomes were postoperative mortality and drainage-related cholangitis.
Results: Eight systematic reviews with meta-analysis involving 4812 participants from 2478 screened reports were identified, including three reviews assessing the use of PBD and five reviews comparing

PTBD with EBD. All original studies included in these reviews were observational retrospective studies. Quality of data abstraction and statistical methods varied across reviews. All systematic reviews had high risk of bias according to ROBIS tool (assessment for risk of bias in systematic reviews). About the use of PBD, three reviews consistently showed that PBD did not decrease postoperative mortality, by contrast, two of these three reviews demonstrated PBD significantly increased overall postoperative morbidity and postoperative infectious morbidity ($p < 0.05$). About the route of PBD, two reviews pointed towards significantly lower drainage-related cholangitis rates (RR, 0.49; 95% CI 0.36–0.67 from the largest review) and overall drainage-related morbidity in PTBD group compared to EBD group ($p < 0.05$), but this superiority of PTBD disappeared in other two reviews. The drainage-related pancreatitis rates were frequently higher in EBD group ($p < 0.05$). EBD groups had longer 1-year, 5-year, and overall survival ($p < 0.05$).

Conclusion: Although the evidence base is still inconclusive, our study suggests that PBD does not decrease postoperative mortality and is therefore not recommended routinely. PTBD results in lower drainage-related morbidity but is associated with lower overall survival compared to EBD in pCCA patients. Large sample sizes and/or international multicentre randomised controlled trials are urgently needed to assess the value of PBD in surgical management of patients with pCCA.

THU294

Imprints of post-liver transplantation: HCV recurrence on immune cell compartment persist despite achieving therapy-induced SVR

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Background and Aims: Recurrence of hepatitis C virus (HCV) in liver transplanted patients has occurred in almost all patients who were viremic at the time of transplantation. Now that it is possible to achieve sustained virologic response (SVR) in post-liver transplant patients at a comparable frequency to pre-transplanted patients, we aimed to comprehensively characterize immune cell subsets after liver transplantation in patients receiving DAA therapy. Particularly, we aimed to define potential immune correlates which could have impact for the risk to develop rejection episodes associated with HCV clearance.

Method: Peripheral blood mononuclear cells isolated from blood samples of liver transplanted patients during DAA therapy (n = 18) were assessed for phenotypes and distribution of both the myeloid and lymphoid immune cell subsets. Patients received mainly calcineurin inhibitors as the backbone immune suppressant. Results were compared to data from healthy (n = 10) and non-transplanted chronic HCV infected (n = 10) patients. Furthermore, in-vitro functionalities of virus-specific CD8+ T cells were investigated in these groups.

Results: Liver transplanted patients with recurrent HCV infection displayed distinct enrichment of CD16+ classical monocytes, myeloid dendritic Cells (mDC), myeloid derived suppressor cells (MDSC), NKG2C+ NK cells and functional (CD45RO+/IL-17+/TNF+) CD4+CD127-$CD25^{high}$ regulatory T cells (Tregs) as compared to healthy controls and non-transplanted chronic HCV infected patients. In contrast, distribution of MAIT cells, plasmacytoid dendritic cells (pDC) and IFN-y producing NK cells were reduced in liver transplanted patients. Importantly, clearance of HCV post-liver transplantation did not significantly alter the phenotypes and distribution of any of the analysed immune cell subsets. In addition, the in-vitro frequency and functionality of HCV-specific CD8+ T cells were also not significantly altered despite achieving SVR after liver transplantation.

Conclusion: Our data indicate that the HCV specific imprints on immune cell parameters post-liver transplantation are not reversed by therapy-induced HCV elimination. This is in line with the clinical observation that cure of HCV post-transplantation did not trigger rejection episodes in many patients.

THU295

The FOXO1-hedgehog signaling axis regulates NLRP3 inflammasome activation in liver ischemia and reperfusion injury

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Background and Aims: Foxo1 signaling plays important roles in cell metabolism, oxidative stress, inflammation, and apoptosis. Activation of the Hedgehog/Gli pathway regulates cell growth, differentiation, and immune function. However, it remains unknown whether Foxo1 may modulate the Hedgehog/Gli pathway in liver ischemia and reperfusion injury (IRI). This study investigated the functional roles and regulatory mechanisms of myeloid Foxo1 signaling in IR-triggered liver inflammation.

Method: Myeloid specific Foxo1 knockout ($Foxo1^{M\text{-}KO}$), β-catenin knockout ($\beta\text{-catenin}^{M\text{-}KO}$), floxed Foxo1 ($Foxo1^{FL/FL}$) or β-catenin ($\beta\text{-catenin}^{FL/FL}$) mice (n = 6/group) were subjected to 90 min partial liver warm ischemia followed by 6 h of reperfusion. In parallel *in vitro* study, Bone marrow-derived macrophages (BMMs) were isolated from these conditional knockout mice and transfected with CRISPR/Cas9-mediated Gli1 or Snail knockout vector followed by LPS (100 ng/ml) stimulation.

Results: Mice with myeloid-specific Foxo1 knockout ($Foxo1^{M\text{-}KO}$) were resistant to IR-induced hepatocellular damage, with reduced serum ALT levels, cell apoptosis, macrophage/neutrophil infiltration, and pro-inflammatory mediators compared to the Foxo1-proficient ($Foxo1^{FL/FL}$) controls. Unlike in the $Foxo1^{FL/FL}$ controls, $Foxo1^{M\text{-}KO}$ enhanced β-catenin, the hedgehog signaling effector Gli1, and Snail but reduced NLRP3/caspase-1 activation in ischemic livers. Disruption of Gli1 in $Foxo1^{M\text{-}KO}$ livers deteriorated liver function with reduced Snail while enhancing NLRP3/caspase-1 activity. In parallel *in vitro* studies, we found that macrophage Foxo1 and β-catenin co-localized in the nucleus. The Foxo1-β-catenin interaction reduced Gli1 activation while CRISPR/Cas9-mediated Gli1 knockout diminished Snail and augmented NLRP3/cleaved caspase-1 expression, and IL-1β release in LPS-stimulated macrophages.

Conclusion: Myeloid-specific Foxo1 deficiency activates the Hedgehog/Gli signaling and mitigates IR-induced hepatocellular injury through disruption of competitive binding to β-catenin in the nucleus. Myeloid Foxo1 deficiency diminishes the Foxo1-β-catenin interaction, which in turn enhances β-catenin-TCF/LEF binding and activates the Hedgehog/Gli/Snail signaling leading to inhibited NLRP3-driven inflammatory response. Our findings underscore the crucial role of myeloid Foxo1 signaling in liver inflammatory injury and imply the therapeutic potential in organ IRI and transplant recipients.

THU296

Mesenchymal stem cells-derived extracellular vesicles carried lncRNA-CEP95 ameliorates acute liver rejection by modulating phenotype of natural killer cells

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Background and Aims: Acute rejection remains a major risk factor for graft and recipient survival after liver transplantation. Management of acute rejection mainly rely on immunosuppressive agents, but the therapy is ineffective in about ten percent of the patients. Thus, development of new treatment is required to improve post-transplant survival. Natural killer (NK) cells are important component of lymphocytes resident in liver, yet their role in acute rejection is not completely understood. Mesenchymal stem cells derived extracellular vesicles (MSC-EVS) have been shown to exhibit immunomodulative effect on immune cells including NK cells. This study aimed to examine whether MSC-EVs could ameliorate acute liver rejection by regulating the function of NK cells.
Method: Adult male Brown-Norway (BN) to Lewis rat liver transplantation was performed as a model of acute liver rejection. Extracellular vesicles from human umbilical cord-derived mesenchymal stem cells were isolated. Intravenous MSC-EVs or PBS were administered immediately after transplantation. Liver histology, serum liver function test, pro-inflammatory and anti-inflammatory cytokines were compared. Flow cytometry and immunochemistry staining was performed to study the functional status of CD56-positive NK cells. RNA-seq of MSC-EVs was performed to identify enriched long non coding RNA and its mechanism in MSC-EVs induced protection from acute rejection. *In vitro*, NK cells were incubated with MSC-EVs.
Results: Rats treated with MSC-EVs had a better survival rate and reduced Banff score compared with PBS control group. Serum alanine aminotransferase, aspartate aminotransferase, total bilirubin, and level of pro-inflammatory cytokines (IFN-γ, IL-6) were significantly lower after treated with MSC-EVs, while level of anti-inflammatory cytokines (IL-10, TGF-β) was increased. Flow cytometry and immunochemistry analysis indicated higher percentage of activating NK cell receptors (NKp30, Nkp44) and lower percentage of inhibitory receptor (NKG2A) of intrahepatic NK cells in MSC-EVs treated group. To elucidate possible mechanism, RNA-seq screening was performed and it was revealed that lncRNA CEP95 is enriched in MSC-EVs. RNA pulldown confirmed that LncRNA CEP95 binds with miR-149-5p in NK cells. Upregulated mRNA expression of IL-10 and downregulated expression of IFN-γ in NK cells transfected with lncRNA CEP95 or incubated with MSC-EVs.
Conclusion: This study revealed that extracellular vesicles derived from mesenchymal stem cells ameliorate acute liver rejection by impairing the functional status of NK cells, via upregulating inhibitory receptors of NK cells. This phenotype conversion of NK cells is mediated by MSC-EVs delivered LncRNA CEP95. In sum, our data suggests a new therapeutic strategy for treatment of acute liver rejection by MSC-EVs.

THU297

Hepatic ischemia induces a time-dependent increase in SERPINB3 gene expression

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Background and Aims: Understanding the mechanisms of liver ischemia injury and developing strategies to counteract this injury will reduce acute complications in liver transplantation thus expanding the potential pool of usable donor grafts. The inflammatory response to hepatic ischemia is associated with an increase in cytokine production, leading to liver injury. Recently, SerpinB3, that is undetectable in normal liver, has been reported to be induced by oxidative stress in hypoxic conditions and to determine cell death resistance by the inhibition of apoptosis and increase of cell proliferation.
The aim of the present study was to investigate whether acute liver ischemia might affect the molecular expression of SerpinB3 in relation to inflammatory cytokines profile in the liver.
Method: Male Wistar rats (n = 15) were subjected to partial-hepatic ischemia (60, 120, 180 min) by clamping the hepatic artery and the portal vein; sham operated rats (n = 12) were used as control group. At the end of the procedure, liver and blood samples were collected. Hepatic enzymes were analyzed in serum, while gene expression of SerpinB3 and inflammatory cytokines were assessed in the liver.
Results: Liver ischemia injury was confirmed by increased hepatic enzymes (ALP, ALT, γGT) in the ischemia treated group, compared to the sham group.
Hepatic ischemia induced a progressive and significant increase of SerpinB3 expression, reaching a peak (18 fold increase) at 180 min, while the increase of inflammatory cytokines occurred earlier. In detail, for NOX2 and IL1B the peak expression was observed at 60 min, while IL6 and TNFα peaks occurred at 120 min. No significant modifications were observed in the liver of sham-operated rats.
Conclusion: The present data demonstrate that SerpinB3 is increased in ischemic liver, but its late induction, compared to inflammatory cytokines, might explain the inefficient protection in hepatic ischemia. Early administration of SerpinB3-based compounds might be considered as new potential strategies to counteract this injury.

THU298

Esomeprazole attenuates hepatic ischemia/reperfusion injury by modulation of TLR4-mediated signaling in mice

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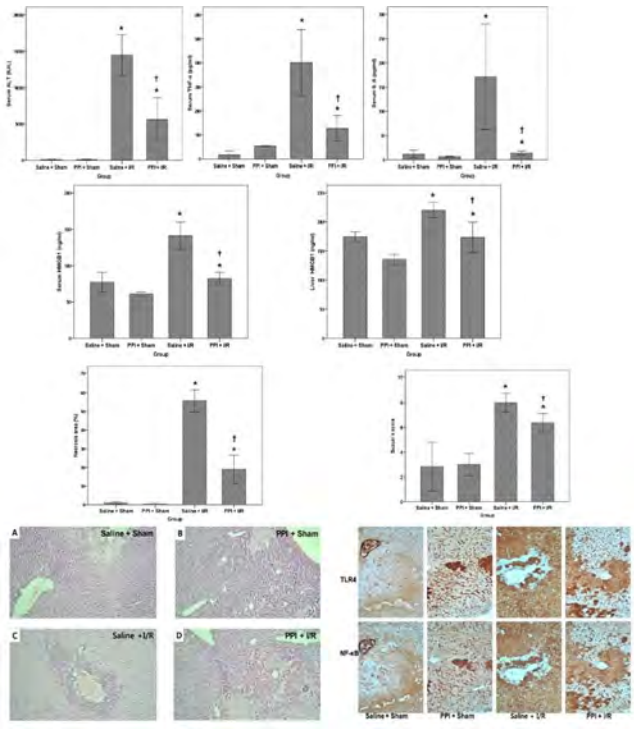
Background and Aims: Recent studies have shown that proton pump inhibitors (PPIs) have a protective effect on various experimental ischemia/reperfusion models, but little is known about its effect on the liver. The aim of this study was to evaluate the beneficial effects of PPI in an experimental model of hepatic I/R injury, focusing on TLR4-mediated signaling, which has been implicated in the development and progression of hepatic I/R injury.
Method: Twenty-four male wild-type (C57BL/6) mice were randomized into four groups: saline + sham, saline + I/R, PPI+ sham, and PPI + I/R. A proton pump inhibitor, esomeprazole, was intraperitoneally injected 30 minutes prior to surgery. The animals were subjected to 60 min of partial warm ischemia (70%), followed by reperfusion for 6 h on the same day. The ischemic lobe of the liver was harvested for hematoxylin and eosin (H&E) stain, western blot and immunohistochemical analyses. Blood was collected and levels of alanine aminotransferase (ALT), proinflammatory mediators and High mobility group box 1 (HMGB1) were measured.
Results: Pretreatment with esomeprazole attenuates hepatocellular injury after hepatic I/R. Pretreatment with esomeprazole decreased production of I/R induced proinflammatory mediators (such as IL-1β and TNF-α) in serum. Pretreatment with esomeprazole suppresses HMGB1 release in serum and ischemic liver after hepatic I/R. Esomeprazole suppresses TLR4-mediated signaling pathway in hepatic I/R. After hepatic I/R, the expression of TLR4, HMGB1, TNF-α, and NF-κB was up-regulated in the Saline + I/R group, but pretreatment with esomeprazole markedly down-regulated the expression of TLR4, HMGB1, TNF-α, and NF-κB in the PPI + I/R group.



Conclusion: Proton pump inhibitor, esomeprazole attenuates hepatic I/R injury by down-regulation of the TLR4-mediated signaling pathway. Esomeprazole can be considered as an agent for use in clinical treatment of hepatic I/R injury.

THU299

MSC-EVs induce liver transplantation tolerance by promoting CD8 +CD28- T cells differentiation and immunomodulatory function via lncRNA MALAT1/IRF4 signaling

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Background and Aims: Liver transplantation is the optimal treatment option for end-stage liver disease. Otherwise, it is generally accepted that the side effects of modern immunosuppression drugs remain a significant contributing factor for less satisfactory long term outcomes. It is reported that a high frequency of $CD8^+CD28^-$ T cells, a special subset of regulatory T cells (Treg), contributes to maintaining stable graft function and reducing immunosuppressant dosage after liver transplantation. We previously found that mesenchymal stromal cells (MSCs) could effectively enhance the immunomodulatory function of $CD8^+CD28^-$ T cells. The possible effective components suggest to be MSC-derived extracellular vesicles (MSC-EVs). However, it is unknown whether MSC-EVs could induce transplantation tolerance by affecting the functional status of $CD8^+CD28^-$ T cells.
Method: Livers from DA rats were transplanted into Lewis rats. Allografts either untreated or treat with MSC-EVs. Liver inflammation, apoptosis, cytokine, and the exchange of sub-population of T cell were compared. We applied RNA-seq screening and identified the mRNA enriched in MSC-EVs, and proved the mechanisms of MSC-EVs induced immunosuppression post-transplantation.
Results: MSC-EVs reduced mortality of rats after liver transplantation by increasing the proportion of $CD8^+CD28^-$ T cells. The concentration of IL-10 and TGF-β was significantly increased in MSC-EVs injection group, while inflammatory factor IL-1β was decreased extremely. MSC-EVs inhibited apoptosis and promoted immunosuppressive function by promoting glucose metabolism of $CD8^+CD28^-$ T cells. MSC-EVs could induce the formation of tolerogenic DCs (tolDCs) and promote the phenotypic transformation of $CD8^+CD28^+$ T cells to $CD8^+CD28^-$ T cells, thus promoting the differentiation regulation and functional activity of $CD8^+CD28^-$ T cells. Mechanically, we applied RNA-seq screening of MSC-EVs and identified the enrichment of LncRNA MALAT1. MSC-EVs might have positive effects on, not only improving the statement of glycometabolism in $CD8^+CD28^-$ T cells, also promoting DCs converse to tolDCs, via LncRNA MALAT1 -miR-125b -IRF4 axis. Luciferase assay showed that down-regulated LncRNA MALAT1 in MSC-EVs could not competing antagonise miR-125 binding to IRF4 in T cells and DC cells, suggested that LncRNA MALAT1 served as ceRNA of miR-125 in activation of IRF4 signaling.
Conclusion: MSC-derived EVs induce the formation of immune tolerance by increasing the proportion of $CD8^+CD28^-$ regulatory T cells. MSC-EVs improve the statement of glycometabolism to reduce apoptosis in $CD8^+CD28^-$ T cells, and promote phenotype conversion from DCs to tolDCs via up-regulating IRF4. LncRNA MALAT1 in MSC-EVs performed as ceRNA towards miR-125 so as to activate IRF4 signaling. This work provides a new strategy for inducing liver transplantation tolerance by MSC-EVs.

THU300

Extracellular vesicles derived from human umbilical cord mesenchymal stem cells alleviate hepatic ischemia-reperfusion injury by regulating neutrophils polarization and suppressing neutrophil extracellular traps formation

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Background and Aims: As a result of organ retrieval, cold storage and warm ischemia during surgery, hepatic ischemia reperfusion injury (HIRI) is an important cause of functional failure after liver transplantation, which is one of the most challenging problems in the field of organ transplantation. Evidences demonstrate that neutrophils play a crucial role in the initiating response to sterile inflammation in HIRI. Extracellular vesicles (EVs) derived from mesenchymal stem cells (MSCs) attract widespread attention in liver pathology because they exert therapeutic effects on immunoregulation and tissue repair. However, the efficacy and underlying mechanisms of MSC-EVs based treatment in immunoregulation of neutrophils in HIRI remain unclear.
Method: Extracellular vesicles derived from human umbilical cord mesenchymal stem cell (huc-MSC-EVs) were isolated and characterized. In vivo, a murine model of 70% hepatic ischemia reperfusion injury was used to explore whether huc-MSC-EVs protected hepatic function via modulating neutrophils polarization and neutrophil extracellular traps (NETs) formation. In addition, mouse primary neutrophils were isolated from bone marrow of tibias and femurs by using density gradient centrifugation and co-cultured with huc-MSC-EVs in vitro.
Results: In vivo, we found that NETs form in the sinusoids of mouse ischemic liver lobes. Treatment with huc-MSC-EVs protected against IRI-induced hepatic apoptosis, associated with decreasing serum levels of ALT, AST, ALP and myeloperoxidase (MPO)-DNA complexes, less tissue level of citrullinated-histone H3, converse ratio of N1/N2 neutrophils subtypes, compared to control mice. In vitro, co-culture of mouse bone marrow-derived neutrophils with huc-MSC-EVs showed that neutrophils was induced into N2 phenotype and performed less NETs formation, in which decreasing levels of MPO-DNA complexes was detected. Meanwhile, we found that both the mRNA and protein levels of IRF4 in N2 phenotype neutrophils increased, and siRNA-mediated knockdown of IRF4 in bone marrow-

derived neutrophils increased N1/N2 ratio and promoted NETs formation. These implied huc-MSC-EVs might regulated immunocompetence of the neutrophils via IRF4 signaling pathway.
Conclusion: In summary, huc-MSC-EVs alleviate HIRI by inducing neutrophil N2 subtype differentiation and reduces NETs. These findings provide a new theoretical basis to promote MSC-EVs based treatment in liver transplantation application.

THU302
Inhibition of gamma-glutamyl transpeptidase ameliorates hepatic/reperfusion injury in rats with fatty liver
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Background and Aims: Fatty liver or steatosis is a condition of excessive fat deposition in the liver with increased γ-glutamyl transpeptidase (γ-GT) levels. Ischemia/reperfusion (IR) injury is a pathological condition with several deleterious effects. We evaluated the protective effects of a specific inhibitor of γ-GT in experimentally induced IR injury in rats with steatosis.
Methods: The portal vein and hepatic artery of left lateral and median lobes were clamped to induce ischemia. Before clamping, 1 ml of saline (IR group) or 1 ml saline containing 1 mg/kg body weight of GGsTop (γ-GT inhibitor) (IR- GGsTop group) was injected into the liver from inferior vena cava. The blood flow was restored at 30 min after the start of ischemia. Blood was collected before and at 30 min after ischemia, and at 2 h and 6 h after reperfusion. All the animals were euthanized at 6 h and the livers were collected.
Results: Treatment with GGsTop resulted in significant reduction of serum ALT, AST, and γ-GT levels and hepatic γ-GT, malondialdehyde, TNF-α, and 4-hydroxynonenal content at 6 h after reperfusion. Inhibition of γ-GT produced marked elevation of serum and hepatic glutathione levels. There was prominent hepatic necrosis in IR group, which is significantly reduced IR-GGsTop group.
Conclusions: Inhibition of γ-GT with GGsTop significantly increased serum and hepatic glutathione levels, reduced hepatic MDA and 4-HNE levels, and remarkably ameliorated hepatic necrosis after reperfusion. The results indicated that GGsTop might serve as an appropriate therapeutic agent to reduce IR-induced liver injury and related events in obesity.

THU303
Influence of PML, RASSF6 and NLRP12 on growth and recurrence of human hepatocellular carcinoma
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Background and Aims: Human hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide. Limited therapy options are coupled with bad prognosis and for HCC recurrence post-liver transplantation, there is no cure. PML, RASSF6 and NLRP12 are tumour suppressor proteins involved in cell signalling pathways associated with tumour development and recurrence and for which we could show that they are reduced in expression in tumour tissue in the human HCC. We hypothesize, that their reduced expression impacts tumour growth positively what is investigated using CRISPR/Cas9 knockout in hepatoma cell lines and a chick chorioallantoic membrane (CAM) model. The CAM model is a modern system allowing to investigate tumour growth without a mouse model.
Method: Using CRISPR/Cas9, we generated heterozygote cancer cell lines with a knockout in exon 1 in PML, RASSF6 and NLRP12. Hepatoma cell lines Huh7, Hep3B and HepG2 were transfected and genotyping was performed via PCR and 2% gel electrophoresis. As yet, the Boyden chamber assay was performed in Huh7 by silencing PML to test for the influence on migration potential. These cell lines were further applied in the chick chorioallantoic membrane (CAM) model. Cell lines with and without the knockout generated tumours in the CAM model that were harvested, weighted and measured for tumour growth analysis and comparison of size and weight. The RNA expression was measured via rtPCR.
Results: PML, RASSF6 and NLRP12 expression is reduced in the human tumour tissue as well as *in vivo* in a murine model and *in vitro* in hepatoma cell lines. The generation of heterozygous PML, RASSF6 or NLRP12 knockout cell lines shows reduced expression of the respective genes. So far, functional assays were performed for PML and revealed that reduced PML expression favours cell migration 1.6-fold. PML expression was reduced to 24% in the cell line HepG2, to 27% in the cell line Huh7 and to 43% in the cell line Hep3B. Further in the CAM model, PML shows significant increase in tumour growth ($P \leq 0.02$) after knockout in the cell line HepG2. The relative RNA expression of PML was decreased by up to 73% in the CAM-tumours. Further research is currently being performed on RASSF6 and NLRP12.
Conclusion: Our findings reveal a relevant influence of PML on HCC tumour growth. The effect of the knockout of RASSF6 and NLRP12 on tumour growth, cell proliferation, migration and apoptosis is being further analysed and will be presented.

THU304
Serum glycomics early after liver transplantation relate to graft loss 3 months after liver transplantation independently of early allograft dysfunction
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Background and Aims: Graft loss during the first year after liver transplantation (LT) affects up to 15% of liver grafts, mainly in the first 3 months. Prediction of outcome early after LT is limited by the lack of robust clinical predictors. Early allograft dysfunction (EAD) is related to early graft loss but is not a strong predictor in individual patients. The goal of this work was to define a serum glycomic signature early after LT that is associated with graft loss at 3 months after LT.
Method: A prospective study in an experienced liver transplant center was performed between 1/1/2011 and 28 February 2017. Glycomic analysis using DSA-FACE was applied to serum samples on postoperative day 7. Using Lasso regression, an optimal serum glycomic signature was identified, associated with 3 months graft survival.
Results: A total of 117 patients were included. Graft loss at 3 months occurred in 14 patients (11.9%). The cohort was split in a training (82 without, 9 with graft loss) and a validation set (35 without, 5 with graft loss). The glycomic signature contains 13 glycans, using Lasso regression an optimal model was fitted yielding an AUC of respectively 0.95 and 0.94 in these sets for graft loss at 3 months ($p < 0.001$). Based on the Youden index an optimal cutoff of this biomarker was defined at 0.773. In the complete sample, this showed a sensitivity of 94% (95% CI: 0.891–0.981) and a specificity of 93% (95% CI 0.661–0.998). PPV and NPV were respectively 99.1% (95% CI 0.943–0.997) and 68% (95% CI : 0.491–0.989). Graft loss was associated with increased undergalactosylation (a marker of inflammation) and an increased presence of fucosylated and triantennary glycans, both signs of liver regeneration. According to this cut-off, multivariate logistic regression analysis showed a odds ratio of 70.211 (95% CI

10.876–453.231, p < 0.001) for graft loss at 3 months, independently of the development of early allograft dysfunction.

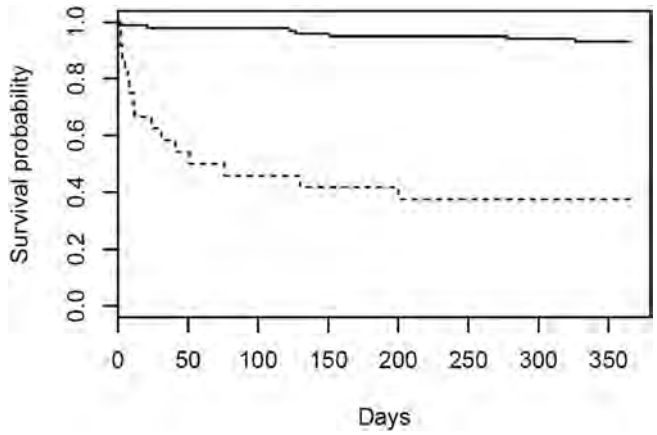

Figure: Full Line: glycomic marker >1.76, Dashed Line: < = 1.76

Conclusion: A serum glycomic signature obtained on postoperative day 7 a after LT is highly associated with graft loss at 3 months after LT. It could guide the clinician in the decision for early retransplantation and thus increase the quality of life and outcome of the patient. It can be applied on routine lab equipment.

THU305

YAP attenuates hepatic ischemia reperfusion injury by inducing autophagy through p38/ERK MAPK pathway

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Background and Aims: Hepatic ischemia-reperfusion injury (IRI) remains a common complication during liver transplantation (LT), partial hepatectomy and hemorrhagic shock in patients. As a key downstream effector of the Hippo pathway, yes-associated protein (Yap) has been reported to be involved in varieties physiological and pathological processes. However, it remains to elusive whether and how Yap may control autophagy activation during IRI.
Method: Human liver tissues from patients undergone LT and control individuals were obtained to evaluate the correlation between Yap and autophagy specific protein LC3. Liver specific Yap knockout ($Yap^{+/-}$) mice and wild type littermates were used to establish IRI model to determine the exact role of Yap in controlling activation of autophagy. In addition, the underlying mechanism of Yap regulating autophagy were further explored.
Results: Yap positively correlates the autophagic level of hepatocytes in patients and autophagy protect against ischemia-reperfusion injury in mice. Knockdown of Yap inhibits hepatocytes autophagy and aggravates ischemic injury through promoting apoptosis both in vitro and in vivo. In addition, Yap deficiency exacerbates mitochondrial damage by increasing ROS production and promotes inflammatory response with more secretion of pro-inflammatory cytokines. Moreover, the regulation of autophagy by Yap during ischemia-reperfusion injury might mediated by p38/ERK MAPK signalling.
Conclusion: We first showed that Yap protects against hepatic ischemia-reperfusion injury by inducing autophagy that suppress the apoptosis of hepatocytes, which enhance the understanding of the roles of Yap during ischemia-reperfusion injury.

THU306

Extracellular vesicles derived from human umbilical cord mesenchymal stem cell protect liver ischemia/reperfusion injury by reducing CD154 expression on CD4+ T cells via CCT2.

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Background and Aims: Liver ischemia/reperfusion injury (IRI) is widely recognized as a major cause of postoperative complications and early hepatic failure after liver transplantation (LT). Intrahepatic CD4+ T cells activation is known to stimulate inflammatory response and hence could aggravate liver IRI progression. We previously showed the therapeutic potential of both mesenchymal stem cells (MSCs) and their extracellular vesicles (EVs) in inflammation-related diseases. The aim of this study is to investigate whether the umbilical cord derived MSC-EVs (UC-MSC-EVs) could modulate CD154 expression on the intrahepatic CD4+ T cells, which consequently alleviate liver IRI, and explore its potential mechanisms.
Method: UC-MSC-EVs were administrated immediately through peripheral vein after the administration of mouse liver IRI model, and the mice were sacrificed at early period (6 h) after reperfusion. Serological liver enzymes, pro-inflammatory cytokines in serum and liver tissue, histological changes, hepatic apoptosis and the membranous expression of CD154 on the intrahepatic CD4+ T cells were examined. Moreover, the molecular mechanism of UC-MSC-EVs and the target signaling pathway were further explored in vivo and in vitro.
Results: the expression of CD154 on the intrahepatic CD4+ T cells was significantly elevated in the liver IRI model compared with the normal group, accompanied with the increasing levels of serological liver enzymes, pro-inflammatory cytokines and hepatic injury score. Furthermore, we found that UC-MSC-EVs could suppress CD154 synthesis and expression in CD4+ T cells by targeting Ca2+/calcineurin/NFAT1 signaling pathway. Mechanistically, we identified Chaperonin Containing TCP1 subunit 2 (CCT2) as a mediator of UC-MSC-EVs affecting Ca2+ influx and subsequently suppressing CD154 expression in CD4+ T cells. Consistently, the hepatoprotective and immunoregulative effects of UC-MSC-EVs was partially weakened when CCT2 was depleted in UC-MSCs.
Conclusion: This study highlighted the therapeutic potential of UC-MSC-EVs in attenuating liver IRI. Our finding is the first to show that UC-MSC-EVs could deliver CCT2 to the intrahepatic CD4+ T cells and modulate their CD154 expression via Ca2+/calcineurin/NFAT1 signaling pathway.

Molecular and cellular biology

THU307

Decreased level of KEAP1 and activation of NRF2 contribute to sorafenib resistant in hepatocellular carcinoma

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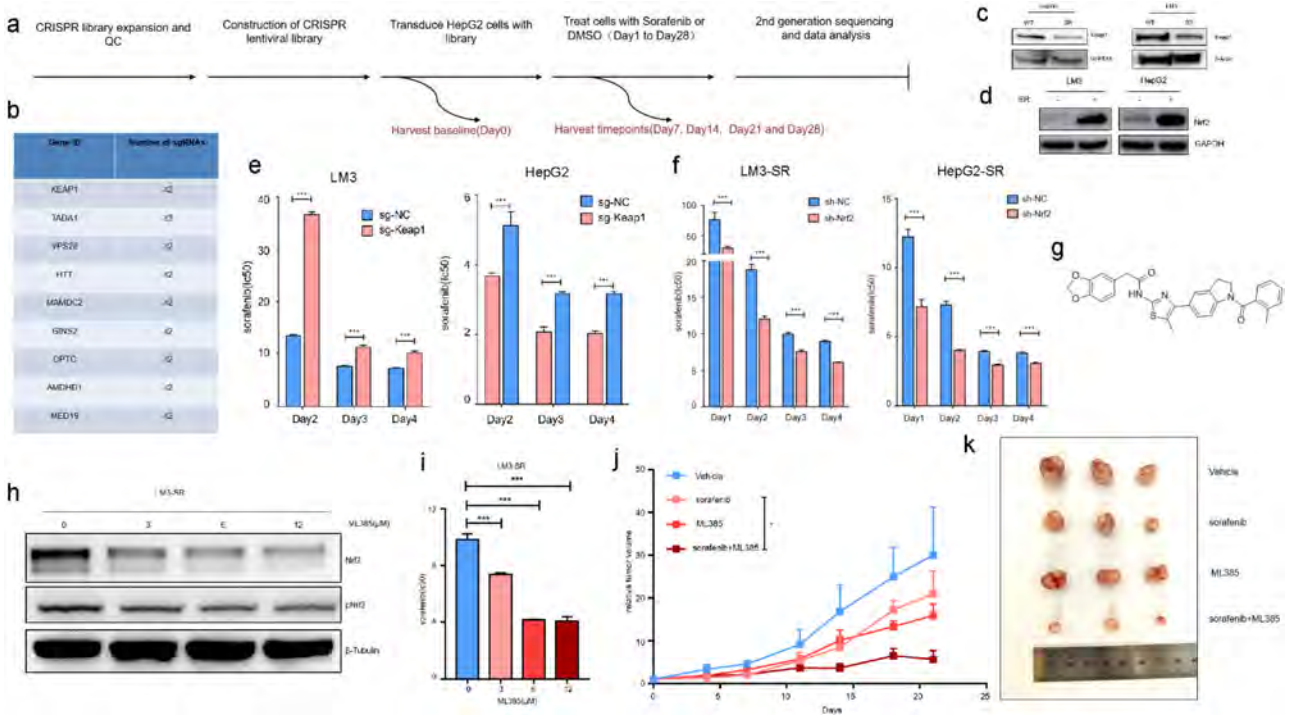

Figure: (abstract: THU307): a. Flowchart of Sorafenib resistance screening; b. Sample list of top ranked genes. c. The protein level of KEAP1 between wild-type HCC cells and sorafenib-resistant HCC cells. WT: Wild Type; SR: Sorafenib Resistant. d. The protein level of Nrf2 between wild-type HCC cells and sorafenib-resistant HCC cells. e. The IC50 of sorafenib in HCC cells after knocking out KEAP1. f. The IC50 of sorafenib in sorafenib-resistant HCC cells after knocking out Nrf2. g. The chemical structure of the Nrf2-specific inhibitor, ML385. h. The protein level of Nrf2 treated by ML385 at different dose in sorafenib-resistant LM3. i. The IC50 of sorafenib in sorafenib-resistant LM3 after treated by ML385 at different dose. j&k. The in vivo combination treatment of ML385 and sorafenib.

Background and Aims: Hepatocellular carcinoma (HCC) in one of the most common malignancies in the world, with multiple resistance and poor prognosis. Sorafenib was the first-time treatment for advanced HCC, but the drug resistance made its efficacy restricted By now, the molecular mechanism of Sorafenib resistance is lack of well understanding.

Method: In this study, by using CRISPR/Cas9 genome library screening, Kelch-like ECH- associated protein-1(KAEP1) was discovered that the decreased Level of KEAP1 contributed to Sorafenib resistance in HCC. And then we exam the function of KEAP1 and its downstream molecule Nrf2 in HCC cell lines.

Results: KEAP1 regulates multiple signaling pathways by ubiquitinating substrate proteins, including nuclear factor erythroid 2-related factor 2 (Nrf2), which are associated with drug resistance of tumor, but the key mechanism of KEAP1 inhibits Sorafenib resistance is unclear. We validate that KEAP1, as an oxidative stress sensor, mediates degradation of Nrf2, thereby conferring sensitivity to Sorafenib; conversely, loss of function of KEAP1, thereby alleviate degradation of Nrf2 and conferring sorafenib resistance. ML385, a Nrf2-specific inhibitor, may increase the sensitivity of Sorafenib in HCC. We examined the combination effect between Sorafenib and ML385 both in vivo and in vitro. We find that ML385 can increase the sensitivity of Sorafenib in sorafenib-resistant cell both in vivo and in vitro.

Conclusion: These studies therefore demonstrate that KEAP1 regulates sensitivity to sorafenib by modulating Nrf2 expression.

THU308

Unravelling the molecular determinants of metabolic syndrome thanks to NMR-metabolomics of urine and serum samples

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Background and Aims: The metabolic syndrome (MetS) can be described as a cluster of metabolic alterations that leads to an increased risk of developing cardiovascular disease, coronary heart disease, stroke and vascular dysfunction. Taking into consideration the definition of the World Health Organization (WHO), MetS is defined as the presence of insulin resistance and other two of the following conditions: obesity (waist circumference or BMI >30 kg/m^2), hyperlipidaemia, hypertension or microalbuminuria. The role of each of the individual factors in the development of the complex syndrome, the effect of alternative molecular definitions of MetS and of the neglected symptomatology (i.e. non-alcoholic steatohepatitis) are not yet clearly understood. MetS has now gained significant importance due to the increasing number of people affected by this pathology. For this reason, the identification of new diagnostic tools and the determination of new biomarkers for the early diagnosis and prognosis of this disorder is now essential.

Method: Metabolomic phenotypes of matched urine and serum samples from over 10,000 adults recruited from a working population in the Basque Country and from a specific project enriched in MetS patients were measured using nuclear magnetic resonance (NMR).

The combined cohort populates all the intermediate stages of the metabolic syndrome with a significant number of individuals.
Results: According to sample metadata, volunteers were classified into the 16 profiles that define the continuous symptomatic transition from the absence of all the risk factors (asymptomatic patients) up to all the subtypes that canonically define the MetS condition. The analysis of the different metabolomic spectra profiles showed clear differences between the different subtypes emphasizing the significant weight of diabetes in the MetS definition. Considering the results of the untargeted analysis, a group of MetS biomarkers were also identified.
Conclusion: Urine alone is able to discriminate patients undergoing metabolic syndrome from healthy individuals. The responsible metabolites for the discrimination agree well with the metabolic pathways often altered in this syndrome. Remarkably, pairwise analysis and statistical distance determination between two given profiles quantifies the contribution of each symptom to the metabolic syndrome. In this context, our metabolic definition of metabolic syndrome best agrees with the one proposed by the WHO.

THU309
The hedgehog effect: mediating crosstalk between liver and adipose tissue

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Background and Aims: As our body and organs form during embryogenesis, different morphogenic pathways influence these processes, one of which is the Hedgehog (Hh) signaling pathway. Despite its crucial role in development, Hh was thought to be inactive in adult organisms for many years, but recently a number of functions in tumorigenesis, organ homeostasis and control of metabolism have been discovered.
In the liver, Hh is highly involved in lipid metabolism and circadian rhythm. Inactivation in hepatocytes causes a severe hepatic phenotype including steatosis, but also influences other organs such as reproductive organs and adipose tissue (AT). Although crosstalk between the liver and AT is known, the role of Hh in this inter-organ communication remains to be elucidated, which is the aim of this study.
Method: Primary hepatocytes and AT – brown (BAT), subcutaneous (SAT), visceral (VAT) – were isolated from mice with hepatocyte-specific inactivation of Hh. The influence of this inactivation was investigated using molecular biological methods such as qPCR. Immunohistochemical markers for BAT were used to conduct immunohistochemistry on AT sections.
Results: Mice with an inactivation of Hh in hepatocytes show a distinct phenotype in liver as well as AT. All types of AT are increased in weight. qPCR analyses show changes in mRNA expression of brown and beige adipocyte markers as well as lipogenesis. An increase of Uncoupled protein-1 (UCP-1)-mRNA in white AT indicates a browning effect. This is supported immunohistochemical stainings revealing stronger innervation as well as clusters of brown hepatocytes emerging in white AT, predominately in VAT.
Conclusion: The morphologic and biochemical changes in mouse AT show the wide influence that hepatic Hh exerts not only in the liver, but also other organs. Browning events occurring in response to inactivation of hepatic Hh could be shown. Although the mechanism that mediates the effects in AT is still under investigation, the results so far show the intriguing role that Hh plays in the liver-AT crosstalk.

THU310
MicroRNA-26b-5p sensitizes hepatocellular carcinoma CD133+ cancer stem cells to cisplatin through downregulation of Jag1-Hes1 and increased BBC3-mediated apoptosis

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Background and Aims: CD133$^+$ cancer stem cells in hepatocellular carcinoma (HCC) are the hallmark of poor prognosis and resistance to chemotherapy. It has been shown that miR-26b-5p regulates HCC EpCAM$^+$ cancer stem cells. We aimed to assess the effect of miR-26b-5p-mediated inhibition of NOTCH signalling on the chemosensitivity of CD133$^+$ cells to cisplatin.

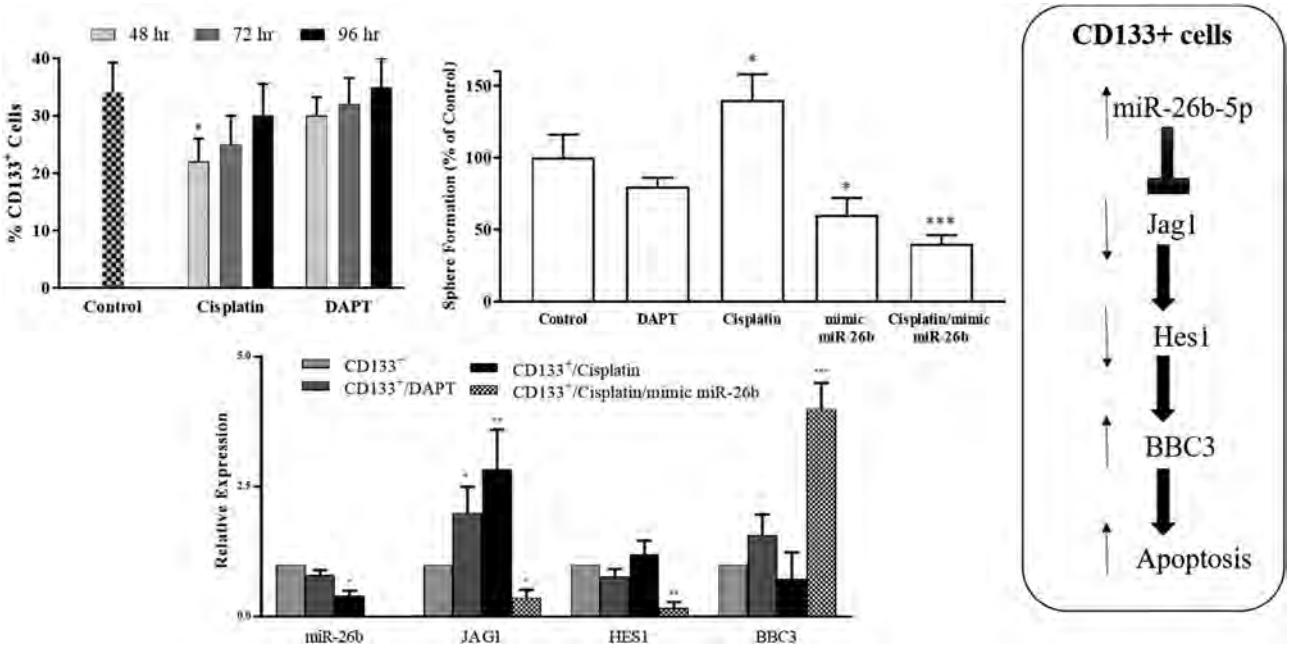

Figure: (abstract: THU310)

Method: Huh7 cells were treated with IC_{50} dose (18 μM) of cisplatin for 48 hr. The $CD133^+$ cells were isolated from untreated and treated cells. Bioinformatics predicted miR-26b-5p targeting JAG1. The expression of miR-26b-5p was assessed using qRT-PCR. $CD133^+$ cells were transfected with mimic and inhibitor of miR-26b-5p, and NOTCH inhibitor γ-secretase DAPT. The cells were analysed for apoptosis by flow cytometry and gene expression of stemness and NOTCH pathway by qRT-PCR. The cell viability and proliferation were analysed by MTT and migration assays. Spheroid formation and self-renewal capacities were assessed in the 3D methylcellulose suspension culture system.
Results: IC_{50} dose of cisplatin decreased $CD133^+$ cells from 35% to 22% ($p < 0.05$). However, cisplatin-resistant $CD133^+$ cells showed upregulation in JAG1, NOTCH1, NOTHC2, NOTCH3, NOTCH4, HES1, and stemness genes SOX2, OC4, and NANOG while significant downregulation in miR-26b-5p compared to untreated and DAPT-treated $CD133^+$ cells. Cisplatin-resistant $CD133^+$ cells formed 30% ($p < 0.05$) more spheroids in 3D culture and had a higher migration capacity than DAPT-treated and untreated $CD133^+$ cells. Mimic miR-26b-5p transfected to cisplatin-treated $CD133^+$ cells led to a significant decrease in cell growth by 45.2% ($p < 0.05$) and enhance apoptosis by 3-fold with 4-fold increased expression of pro-apoptotic BBC3. Cisplatin-treated $CD133^+$ cells transfected with mimic miR-26b-5p formed 39.2% ($p < 0.05$) fewer spheroids and showed decreased expression of JAG1 and HES1 than non-transfected cells.
Conclusion: The upregulation of BBC3 in transfected $CD133^+$ cells was correlated with enhancing the apoptosis rate. MiR-26b-5p-mediated JAG1 downregulation led to a decrease in the expression of HES1. HES1 was reported to negatively regulate BBC3. MiR-26b-5p enhanced sensitivity to cisplatin via enhancing BBC3-mediated apoptosis through downregulation of the JAG1-HES1 axis.

THU311
TMBIM6 regulates ageing and high-fat diet-induced lipid accumulation

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Background and Aims: TMBIM6 is an antiapoptotic protein known to suppress the cell death by regulating ER stress. TMBIM6 contain six transmembrane regions and localize to the ER membranes. TMBIM6 cyto-protective functions conserved in plants and mammals. Our main target to study TMBIM6 effect in high fat diet model and also aging associated fatty liver in normal diet condition. We observed ApoB a lipid transfer protein highly accumulated liver of high fat died (HFD) TMBIM6 KO (knock out) mice after 8 weeks compared to WT (wild type) mice. In addition, we also observed TMBIM6 KO mice aged mice gained body and liver weight and high hepatic triglyceride level when compared with its WT counterparts.
Method: For high fat diet study we categorized TMBIM6 WT and KO mice for HFD model in each group 6 animals. In addition, we also categorized WT and TMBIM6 KO mice into young, middle and old groups, and observed the effect on hepatic lipid accumulation in normal food diet condition. Several Biochemical analysis of the lipid profile, western blotting for the protein expression oxidative stress for the histopathological analysis was performed.
Results: Our result explored that excessive post translational oxidation of protein disulfide isomerase (PDI) intra-ER ROS accumulation and folding capacitance alteration were also observed in HFD-TMBIM6 KO mice, in line the increase in lipid peroxidation level and ROS-induced oxidative stress was observed in TMBIM6 KO aged liver. Loss of TMBIM6 induced excessive ER-mitochondria interactions and high molecular weight complexes of PDI during the aging process. The canonical UPR arms proteins were aberrantly expressed where we observed that the expression of ER chaperone proteins like GRP78 and PDI; ATF6, p-PERK, and p-eIF2 were down regulated and IRE1-mediated JNK signalling was activated in TMBIM6 KO aged liver. In addition to TUNEL positive cells, caspase 7 and 12 were highly activated in TMBIM6 KO mice from the middle to advanced age, suggesting the protective effect of TMBIM6 on aging-induced apoptosis.

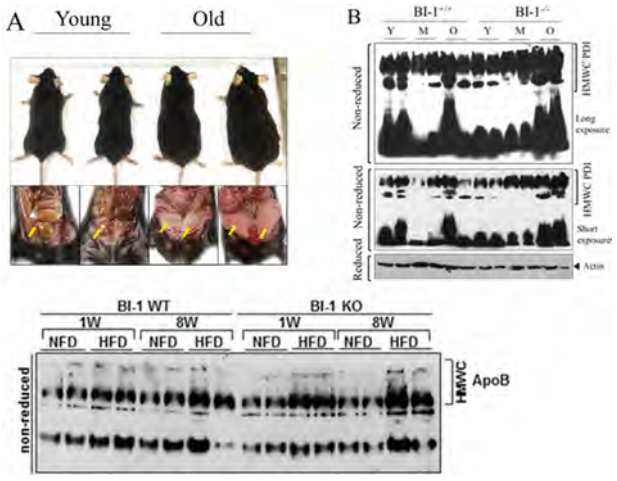

Figure: TMBIM6 regulated hepatic, ApoB secretion and formation of In HFD model. A High fat acculation and Disulfide bonds during oxidative stress aging process.

Conclusion: Our results suggest that TMBIM6 mediated enhancement of ApoB secretion regulates hepatic lipid accumulation in high fat diet condition, likely through regulation of ER stress and ROS accumulation, and also aging-induced fatty liver is regulated by TMBIM6 through the regulation of ER stress and proteostasis.

THU312
Decreased expressions of p70S6 K in NK cells of F4-NAFLD patients inhibited F-actin and was correlated with their impaired function

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Background and Aims: Co-localization of p70S6 K and stress fibers was suggested to regulate actin polymerization as rapamycin treatment could inhibit the elongation and organization of actin stress fibers via inhibition of p70S6 K. We investigated effects of insulin resistance on mTOR signaling pathway of NK cells as a potential cause for their impairment in Nonalcoholic-Fatty Liver-Disease (NAFLD).
Method: Fresh peripheral blood NK cells isolated from healthy volunteers and 72 NAFLD patients (histology documented adults lacking full criteria of metabolic-syndrome), and characterized by flow-cytometry.
Results: Histologic progression of liver injury significantly correlated with elevated pro-inflammatory serum cytokines and insulin resistance. Western blot analysis of NK cells form NAFLD patients with F4 fibrosis showed to have dramatically reduction in PI3 K pathway. ERK/MAP kinase pathway showed also reductions in these patients. Notably, these results were correlated with inhibitions in mTOR, p70S6 K and F-actin phosphorylation ($p = 0.001$). NK stimulations with insulin (physiologic levels) reversed these effects. Compared to normal HOMA NK-cells by *in-vitro* co-culture with HSCs, high-HOMA $CD56^{dim}$ cells (with F3-F4) exhibited increased apoptosis and fail to block HSCs activation. While insulin incubation stimulated NK cell activation and killing of HSCs. Rapamycin reduced $CD56^{dim}$ expressions of insulin receptors (mimicking NAFLD insulin resistance) and prevented the insulin stimulation effect on NK cells.

Conclusion: Systemic Insulin-Resistance in NAFLD also includes the NK cells with reduced expressions of p70S6 K and F-actin and therefore impairment in their function, which leads to cirrhosis and probably cancer.

THU313

A fatty acid amide hydrolase inhibitor, URB597, inhibits MICA and MICB shedding

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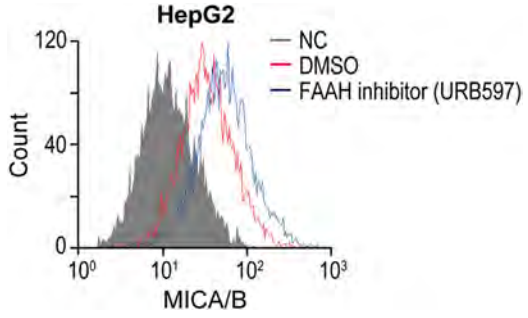
Background and Aims: MHC class I polypeptide-related sequence A (MICA) and MICB are ligands for natural killer group 2, member D (NKG2D) on natural killer cells and T cells, playing an essential role in immunosurveillance system which prevents the tumor initiation. We previously identified that MICA is an HCC-susceptible gene by genome-wide association study. However, proteolytic cleavage of MICA/B protein releases soluble MICA/B, which works as a decoy for NKG2D, leading to the evasion of tumor cells from immune system. Thus, prevention of MICA/B shedding is crucial for the immune surveillance-mediated prevention of HCC. Here, we report screening results identifying a protease inhibitor, which inhibits MICA/B shedding.
Method: Cell surface MICA/B levels were determined by flow cytometry. Protease inhibitor library was used for identifying the regulators for MICA/B shedding. Nano-luciferase reporter-tagged MICA was used to estimate the soluble MICA levels. *In vitro* cleavage assay and transcriptome analyses were done using recombinant MICA protein and cDNA arrays, respectively. Lentiviral vectors were used to establish cells stably expressing FLAG-tagged fatty acid amide hydrolase (FAAH) and those expressing TIMP3 specific short hairpin RNA.



Results: Out of 53 kinds of proteinase inhibitors, MMP inhibitor increased MICA/B levels on the surfaces of HepG2 and Hep3B cells, consistent with previous reports. Further, it was newly found that cell surface MICA/B proteins levels were significantly increased after the treatment of URB597, an FAAH inhibitor. In contrast, levels of soluble MICA were suppressed by URB597. Because MICA/B mRNA levels were not increased by URB597, it was suggested that URB597 prevented the shedding of MICA/B from the cells and increased its levels on the cell surface. Because URB597 did not have direct effects on MICA/B cleavage in an *in vitro* cleavage assay, the effects seemed indirect. Genome-wide cDNA array suggested that TIMP3 gene expression may be involved in the prevention of MICA/B shedding. Indeed, knockdown of TIMP3 led to promotion of MICA/B shedding without affecting the transcriptional activity of MICA/B. Further, overexpression of FLAG-tagged FAAH resulted in suppression of TIMP3 expression and the promotion of MICA/B shedding.
Conclusion: An FAAH inhibitor, URB597, prevents the shedding of MICA/B proteins through the activation of TIMP3. Because preventing MICA/B shedding from HCC cells theoretically leads to excluding those cells by immune system, treatment of FAAH inhibitor may have preventive effects against HCC. Because FAAH inhibitor is already in clinical trials for the therapeutics of other diseases, further analyses may warrant its use by a drug repositioning for the prevention of HCC.

THU314

A trans-activator of transcription-fusion bone morphogenetic protein 7 polypeptide suppresses CCL4 induced-hepatic fibrogenesis in mice

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Background and Aims: Hepatic fibrosis results in cirrhosis, liver failure, and portal hypertension and often requires liver transplantation. Transforming growth factor-beta (TGF-b) signaling plays a pivotal role in liver fibrosis by activating hepatic stellate cells and inducing hepatic cell death. Bone morphogenetic protein (BMP)-7, a member of the TGF-beta superfamily, is an endogenous antagonist of TGF-β. In this study, we examined whether trans-activator of transcription (TAT)-fusion BMP-7 polypeptide, the prodrug of BMP-7, suppresses TGF-beta signaling and its fibrogenic function in a murine model of liver fibrosis.
Method: A model of liver fibrosis was developed by repeated intraperitoneal injection of hepatotoxic carbon tetrachloride (CCl4) twice per week for up to 12 weeks. To investigate the therapeutic effect of BMP7 prodrug on hepatic fibrosis, mice received the drug at a dose of 0 μg/kg (n = 10; control), 50 μg/kg (low-dose group, n = 8), and 500 μg/kg (high-dose group, n = 10). Liver tissues were snap-frozen in liquid nitrogen or fixed in 4% buffered paraformaldehyde for immunostaining.
Results: The aspartate and alanine aminotransferase levels were significantly decreased in the BMP7 prodrug-treated groups compared to those in the control group (all $P < 0.05$). Hepatocyte apoptosis was significantly decreased in the prodrug-treated groups. Fibrous septa surrounding liver parenchyma and marked bridging portal-to-portal with occasional nodules were clearly seen in the control, while the treated groups showed only fibrous expansion of some portal areas with or without short fibrous septa. According to the Batts scoring system, the fibrotic burden in TAT-BMP7-treated mice was significantly reduced compared to that of control mice (all $P < 0.05$). In the treated groups, the mRNA levels of collagen 1A1, smooth muscle α-actin, and connective tissue growth factor (CTGF) were significantly reduced compared to those in the control group (all $P < 0.05$).
Conclusion: Our data demonstrate that TAT-BMP7, a prodrug of BMP7, can reduce hepatic fibrosis by suppressing TGF-beta signaling.

THU315

Dickkopf-1 enhances tumourigenic potential by inducing liver angiogenesis

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Background and Aims: Dickkopf-1 (DKK-1) is an antagonist of Wnt signalling. Several reports have shown that DKK1 is overexpressed in hepatocellular carcinoma (HCC) tissue and that a high serum DKK1 level is an unfavourable prognostic factor in patients with HCC. Here, we explored the role played by DKK-1 in hepatocarcinogenesis using HCC cell lines and xenograft mouse models. We used the clustered regularly interspaced short palindromic repeats (CRISPR)-associated endonuclease Cas9 system to modulate DKK-1 expression.
Method: Cell lines Huh7 and Hep3B, which express DKK-1 at low and high levels, respectively, were used. The CRISPR/Cas9 system was employed to create a Tet-on Huh7 cell line (in which DKK-1 expression was tetracycline-inducible) and a DKK-1 knockout line (KO Hep3B). The angiogenic potential of human umbilical vein endothelial cells (HUVECs) was investigated using the tube formation assay. In addition, the effects of DKK-1 knockdown on tumour growth and angiogenesis were explored in subcutaneous Hep3B- and DKK1-KO Hep3B-tumour xenograft mouse models.
Results: The angiogenic potential of HUVECs significantly increased after treatment with human recombinant DKK-1. The expression level of proteins (as measured by ELISA) secreted from Tet-on Huh7 cells was higher than that secreted from the corresponding control cells, while the expression level of proteins secreted from KO Hep3B cells was lower than that secreted from the corresponding control cells. When HUVECs were treated with Tet-on/off Huh7- and KO Hep3B-conditioned media in an indirect two-dimensional co-culture system, Tet-on Huh7 medium increased the angiogenic potential of HUVECs, whereas Tet-off Huh7 and KO Hep3B media did not. At 6 weeks after xenograft, DKK1-KO Hep3B implantation-induced tumours in mice were smaller than Hep3B implantation-induced tumours in control mice. Although tumour volume did not differ significantly between groups, the tumour weight was lower in the DKK1-KO Hep3B group than in the Hep3B group. Additionally, the level of DKK-1 protein (pDKK-1) secreted in DKK1-KO mice was less than that secreted in control mice, as confirmed by ELISA.
Conclusion: DKK-1 may enhance tumourigenesis by inducing angiogenesis; DKK-1 may serve as a potential therapeutic target.

THU316
The FXR agonist obeticholic acid decreases matrix metalloproteinase activity via RECK and TIMP modulation in hepatic ischemia/reperfusion injury

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Background and Aims: We have recently shown a reduction in the activity of matrix metalloproteinases (MMPs) by the farnesoid X receptor (FXR) agonist obeticholic acid (OCA) in liver submitted to ischemia/reperfusion (I/R). Inducible NOS (iNOS) is known to regulate the MMP activity in I/R injury and we have previously documented the ability of OCA to decrease iNOS content in I/R-treated rats. The reversion-inducing-cysteine-rich protein with kazal motifs (RECK), an MMP modulator, was found to be a novel transcriptional target of FXR. In this study, we evaluated the effects of OCA on RECK and tissue inhibitors of metalloproteinases (TIMPs) content, MMP activity and iNOS expression in liver after I/R.
Method: Male Wistar rats (n = 20) were orally administered 10 mg/kg/day of OCA (Intercept Pharmaceuticals) for 5 days or vehicle and subjected to a 60-min partial hepatic ischemia or sham-operated. After a 60-min reperfusion, tissue samples were collected for RECK,

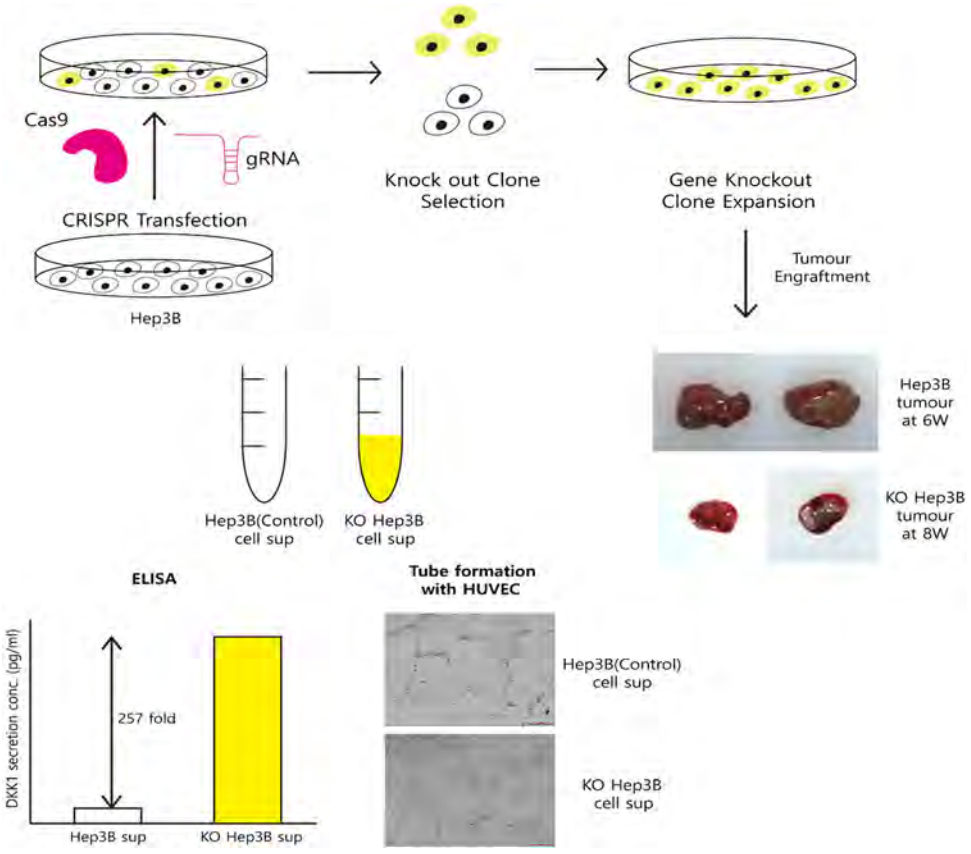

Figure: (abstract: THU315)

TIMP-1, TIMP-2 and iNOS expression by Western blot analysis and MMP-2 and MMP-9 analysis by zymography. Serum levels of AST and ALT as well as total and direct bilirubin were also quantified.
Results: I/R induced a decrease in liver RECK and TIMPs expression. These changes were concomitant with an increase in MMP-2 and MMP-9 activity. OCA administration increased RECK, TIMP-1 and TIMP-2 and reduced MMP-2 and MMP-9 activity in the liver. An inverse correlation between RECK versus MMP-2 and MMP-9 was found. A positive correlation between MMP-2 and MMP-9 versus iNOS was observed. Furthermore, an inverse correlation between MMP-2 and MMP-9 versus TIMPs was found. Although not significantly, OCA administration reduced hepatic serum enzyme levels in the I/R group, and a significantly lower level of direct bilirubin was detected in the I/R group treated with OCA compared to vehicle-treated I/R rats.
Conclusion: Our results demonstrate the ability of OCA to limit the hepatic activation of MMP-2 and MMP-9 that occurs during liver I/R damage, probably via timely recovery of RECK and TIMPs protein levels. This is supported by an inverse correlation between MMP activity versus RECK and a positive correlation between MMP activity versus iNOS. While further studies will clarify the sequence of alterations and cause-effect patterns, these results suggest that changes in RECK protein may have therapeutic potential in MMP modulation during hepatic I/R damage.

THU317
Cross-linking of liver metabolism - hedgehog as a key regulator of energy metabolism, regulating mechanistic target of rapamycin activity

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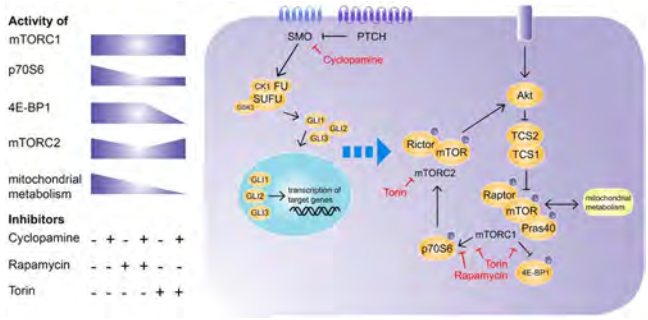
Background and Aims: The Hedgehog (Hh) pathway plays a crucial part in the maintenance of the homeostasis and the regeneration of hepatic tissue. As a consequence, abnormal Hh signalling contributes to various diseases like steatosis and cancer. Both are closely related to alterations in the energy metabolism of the liver. The direct impact of the Hh pathway on these changes is still unclear. The aim of this study was to examine molecular interactions of Hh signaling and another important morphogenetic pathway called the mechanistic target of rapamycin (mTor), which is a main regulator of energy metabolism.
Method: Primary hepatocytes from a hepatocyte specific knockout mouse model with repressed Hh signaling were used to examine the interactions of the Hh and the mTor pathway in liver metabolism. To analyze the interaction of both pathways in detail, in vitro studies with non-transgenic mice were performed using the Hh inhibitor cyclopamine, the mechanistic target of rapamycin complex 1/2 (mTorC1/C2) inhibitor torin, the mTorC1 inhibitor rapamycin and the combinations thereof. The cells were analyzed using Proteome analyses, immunohistochemistry, Western Blotting, flow cytometry, qPCR and Seahorse technology.
Results: Primary hepatocytes from mice with repressed Hh Signaling exhibit an altered energy metabolism with decreased mTor activity and reduced production of adenosine triphosphate. Moreover, the treatment of cells from non - transgenic mice with diverse mTor and Hh inhibitors revealed a close interaction of both pathways. The inhibition of Hh and mTorC1 showed a synergistic effect on the repression of mTorC1 downstream and mTorC2 activity. In addition, our Seahorse analysis demonstrates the same impact of both inhibitors on the functionality of the electron transport chain. However, the combination of Hh and mTorC1 and C2 inhibitors has no additional effect on mTor signaling or energy metabolism.



Conclusion: Our results propose a possible interaction of the Hh pathway with the mTorC2 complex. We hypothesize that Hh signaling may influence the energy metabolism and other cellular responses through the modulation of mTor signaling, building an interacting network of liver metabolism. This opens up new insights into the use of Hh and mTor inhibitors as part of therapeutic intervention in cancerous diseases like the Hepatocellular carcinoma (HCC).

THU318
Functional consequences of metabolic zonation in murine livers: new insights for an old story

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Background and Aims: Zone-dependent differences in the expression of metabolic enzymes along the porto-central axis of the acinus are a long-known feature of liver metabolism. A prominent example is the preferential localization of the enzyme glutamine synthetase in pericentral hepatocytes, where it converts potentially toxic ammonia to the valuable amino acid glutamine. However, with the exception of some key regulatory enzymes, there is still no comprehensive and quantitative assessment of zonal differences based on the abundance of metabolic enzymes and, above all, an assessment of the associated functional differences between portal and central hepatocytes.
Method: We addressed this knowledge gap by establishing an alternative method for the separation of periportal and pericentral hepatocytes based on flow cytometry that yields sufficiently pure cell fractions. Specific marker proteins with no overlap in zonal expression were chosen for intracellular staining and subsequent sorting of isolated primary hepatocytes into pure populations of periportal and pericentral hepatocytes. An antibody against glutamine synthetase (*GLUL*) was used to obtain cells from the pericentral region, whereas cadherin-1 (*CDH1*) was selected to isolate periportal hepatocytes. Quantitative shotgun proteomics identified hundreds of differentially expressed proteins? between the two cell populations. These proteomics datasets were used to extend the kinetic model of central hepatic metabolism, Hepatokin1, to generate portal and central instantiations of the model.
Results: Our analysis indicated that there are significant differences in the abundance of two-thirds of metabolic enzymes between periportal and pericentral hepatocytes. Modeling of the proteome profiling data suggested that the functional differences implied by unequal enzyme abundances along the porto-central axis depended essentially on the actual plasma concentrations of metabolites and hormones. For example, despite large zonal differences in the capacity of the urea cycle and glutamine synthesis, significant porto-central differences in the total ammonia-detoxifying capacity are only expected for external ammonia concentrations that are far above the physiological value.

Conclusion: The model simulations revealed significant portal-to-central differences in almost all metabolic pathways, including carbohydrates, fatty acids, amino acids, and detoxification.

THU319

PXB-cells for the study of lipid metabolism: robust and human-specific lipid profile in human hepatocytes freshly isolated from chimeric mice with humanized liver

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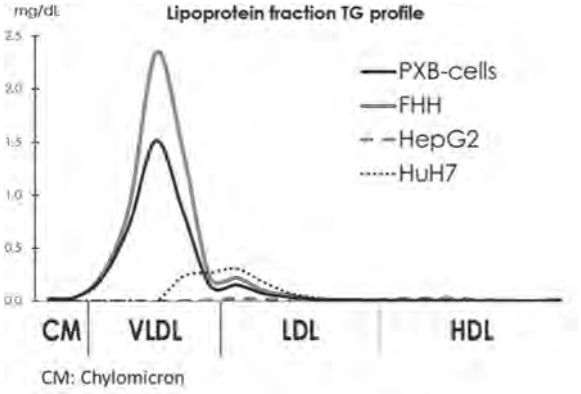
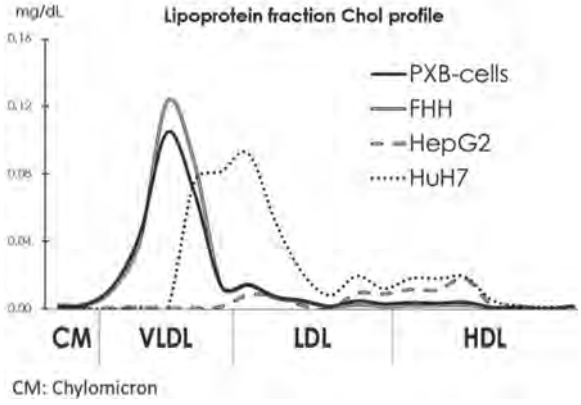
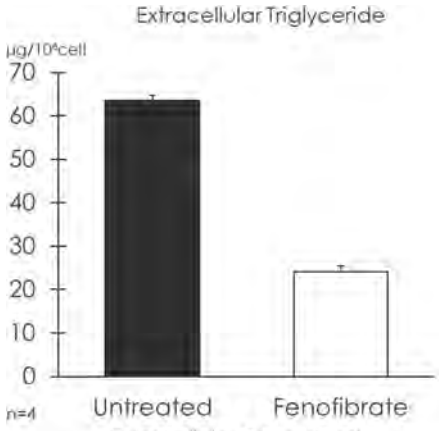
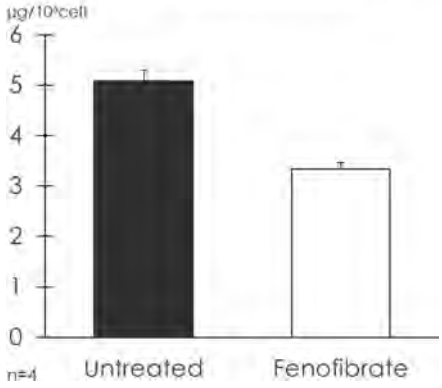
Background and Aims: Dysregulation of lipid metabolism is one of the most common factors in pathogenesis of lifestyle diseases. Restoring lipid metabolism, therefore, represents an attractive therapeutic approach; however, development of therapeutics targeting lipid metabolism pathways is often hampered by species differences. Thus, having research tools that provide human-specific lipid profiles and that are available in a consistent manner is key to R&D success. We have previously demonstrated successful mass production of human hepatocytes freshly isolated from chimeric mice with humanized liver (PXB-cells). Since PXB-cells maintain high levels of human albumin (hAlb) secretion and cytochrome P450 activity in culture, we hypothesized that PXB-cells also maintain human-like lipid profiles. In this study, we investigated the utility of PXB-cells for lipid metabolism-related research in comparison with HepG2, HuH7, and fresh human hepatocytes (FHH).
Method: PXB-cells were cultured in maintenance medium for 8 ~ 13 days and then in analysis medium, which does not contain lipid components, for additional 2 days. To characterize the lipid profile of PXB-cells, extracellular lipoprotein fraction, intra/extracellular lipid content, and lipid metabolism-related gene and protein expression levels were analyzed. HepG2, HuH7 and FHH were evaluated in the same manner. In addition, PXB-cells were treated with antihyperlipidemic agents for 2 days and extra/intracellular lipid components were analyzed.
Results: PXB-cells secreted larger amounts of cholesterol (Chol), triglyceride (TG), hAlb than HepG2 and HuH7. Strikingly, most Chol and TG secreted by PXB-cells were attributed to very low density lipoprotein (VLDL) fraction, which was similar to FHH but in contract to HepG2 and HuH7. In addition, high levels of expression were confirmed for several lipid metabolism-related genes and proteins in PXB-cells. Furthermore, the antihyperlipidemic agents reduced the lipid parameters in PXB-cells.
Conclusion: PXB-cells possess unique characteristics that resemble FHH with the steady supply and the human-like lipid profiles, including high levels of VLDL secretion. In addition, PXB-cells exhibited human-like responses to antidyslipidemic agents. Since PXB-cells maintain high hepatocyte functionality such as drug metabolism, they are a promising *in vitro* research model for the development of drugs targeting the lipid metabolism in the liver.









THU320

Ductular reaction and its microenvironment is aetiology driven

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Background and Aims: Ductular reaction (DR) is observed in the vast majority of chronic liver injuries. This reaction represents the activation of the liver progenitor cells (LPCs) in humans. However, the ductular reaction and its microenvironment are poorly characterised in human liver diseases. In this study, we aim to define an aetiology driven microenvironment of the ductular reaction in acute and chronic liver diseases.
Method: Laser capture microdissection and RNA sequencing of the ductular reaction is performed on snap-frozen tissue (n = 34) from primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), autoimmune hepatitis (AIH), hepatitis C virus (HCV), drug-induced liver injury (TOX) and normal (CTRL) livers. Multiplex staining is performed on an expanded disease cohort (n = 174).
Results: Reduction analysis of the transcriptomic expression levels shows that the DR and its adjacent microenvironment are clustered by disease aetiology. We established a distinctive gene expression signature between the separate diseases regarding the immune microenvironment (e.g. CD9, CD22), the extracellular matrix (e.g. MMP14, collagen type IV) and angiogenesis (e.g. VEGF). Furthermore, a multiplex analysis approach reveals the interacting cells (e.g. T cells, B cells, macrophages) of the ductular reaction by neighbourhood analysis in an aetiology dependent manner.
Conclusion: Our study characterizes an aetiology specific ductular reaction and accompanying microenvironment.

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Increased autophagy is linked to exosomes secretion in ductular cells of cirrhosis

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Background and Aims: Exosomes are vesicles released from cells by fusion of multivesicular bodies (MVB) with plasma membrane. Autophagy has been reported to intersect with biogenesis and secretion of exosomes. This study aimed to investigate whether autophagy regulates exosomes secretion in the context of ductular cells of cirrhosis.
Method: We purified ductular cells from a rat model of AAF/CCL4-induced liver cirrhosis using EpCAM-positive selection. Autophagic flux and MVB pathway were evaluated by Western blot and immunofluorescence staining in ductular cells. Rat bile, a local fluid can represent the secretion of biliary epithelial cells, and the culture supernatants from isolated ductular cells were collected for precipitation of exosomes using ExoQuick™. Exosomes concentration was analysed by nanoparticle tracking system.
Results: Western blot of bile samples confirmed the successful extraction of exosomes by revealing the presence of TSG101, flotillin-1 and CD9 markers. Bile exosomes concentration was found to be higher in normal rat than in AAF/CCL4 rat. *In vitro* experiment also demonstrated that exosomes derived from normal cells have higher abundance compared to exosomes released by ductular cells from AAF/CCL4 livers. To address whether cirrhotic induction of autophagy would promote the interaction of MVB with autophagic structure, ductular cells were incubated with monodansylcadaverine (MDC), an autofluorescent compound that accumulates in autophagic vacuoles, and the fluorescent sphingolipid N-Rh-PE, which efficiently labels MVB. There was increased colocalization of MDC-labeled vacuoles with the N-Rh-PE–labeled MVB in ductular cells from AAF/CCL4 livers, compared to those from normal livers. Interaction between MVB and autophagosome was also confirmed by immunostained for the recycling endosomal marker Rab11 and the autophagosome marker LC3B. A relocation of Rab11-positive vesicles from plasma membrane to the LC3B-positive punctae was observed in ductular cells from AAF/CCL4 livers. Importantly, the decreased exosomes secretion and the increased colocalization of autophagosome with MVB were rescued on silencing of the autophagy regulator ATG7, suggesting autophagy may re-route MVB toward autophagic pathway, hampering exosomes release.
Conclusion: Our findings discovered mechanisms controlling exosome release and identify a process where autophagy crosstalk with the exosomal pathway in liver cirrhosis.

THU322

Screening of components involved in activation of innate immune responses and inflammation in NEMO KO mice

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Background and Aims: Inflammation is a hallmark of chronic liver disease of which the cellular and molecular mechanisms are at present not fully understood. Nonetheless, the inflammasome seems to contribute to the progression and fibrogenic response in several liver diseases. The inflammasome leads to activation of caspase-1 and subsequent maturation of pro-inflammatory cytokines, resulting in pyroptosis and the regulation of cell survival and cell death. While many different signals can activate the NLRP3 inflammasome, hepatocyte mediated activation of the inflammasome is not not well investigated. In our present study, we aim to identify endogenous danger signals responsible for inflammasome activation from dying hepatocytes of $NEMO^{\Delta hepa}$ mice.
Method: To evaluate hepatocyte mediated activation of the inflammasome we used an immortalized macrophage reporter cell line with a constitutively active NLRP3 and ASC-mCerulean tag. These cells were subjected to HPLC fractionated supernatant from isolated $NEMO^{\Delta hepa}$ hepatocytes. Positive fractions were selected and subjected to multiple fractionation steps after which positive fractions were identified by MS and peptides were synthesised. Activity was measured *in vitro* by fluorescence imaging and FACS analysis. RNAseq analysis was used for confirmation of inflammasome activation and pathway analysis.
Results: Stimulation of reporter cells with supernatant from WT or $NEMO^{\Delta hepa}$ hepatocytes resulted in activation of the NLRP3 inflammasome after 3 hour stimulation by the $NEMO^{\Delta hepa}$ but not the WT supernatant. After HPLC fractionation activation of the NLRP3 inflammasome occurred in several fractions after 3 hours of stimulation. After three subsequent fractionation steps 14 peptides were identified by MS from the NLRP3 inflammasome activating fractions. Subsequent synthetisation and stimulation showed that 2 peptides activated the NLRP3 inflammasome, which was in turn confirmed by FACS and RNAseq.
Conclusion: Supernatant from hepatocytes isolated from $NEMO^{\Delta hepa}$ mice activates the NLRP3 inflammasome *in vitro* and this activation can be measured by using a specific reporter cell line. After repeated fractionation, several fractions were still able to activate the NLRP3 inflammasome and as such, positive MS identified fractions were

synthesized. These synthesized peptides could still activate the NLRP3 inflammasome, suggesting possible new endogenous danger signals, derived from dying hepatocytes of NEMO$^{\Delta hepa}$ mice.

THU323

Establishment of murine model of acute-on-chronic liver failure

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Background and Aims: Acute-on-chronic liver failure (ACLF) is characterized by liver failure due to acute hepatic injury on an underlying chronic liver disease, accompanied by acute decompensation, organ failure, and high mortality. Pathophysiology of disease remains unclear, necessitating the need for animal model. In this study, we aim to develop murine model of **ACLF** mimicking characteristics of human ACLF.

Method: Chronic liver injury were induced by i.p. administration of CCl4 (0.1–0.5 ml/kg) in C57BL6 mice (n = 25), acute injury was induced by i.p. administration of LPS (50 µg/kg) and Acetaminophen (350 mg/kg) (fig 1A). Animals were sacrificed at week 10 (n = 5); and at 24hrs, day 7 and day 11 after acute injury, blood was collected, and organs were harvested for histological and IHC analysis.

Results: Liver histology confirmed fibrosis and cirrhosis after 10 weeks of CCl4 injury. No secondary organ damage or ascites were

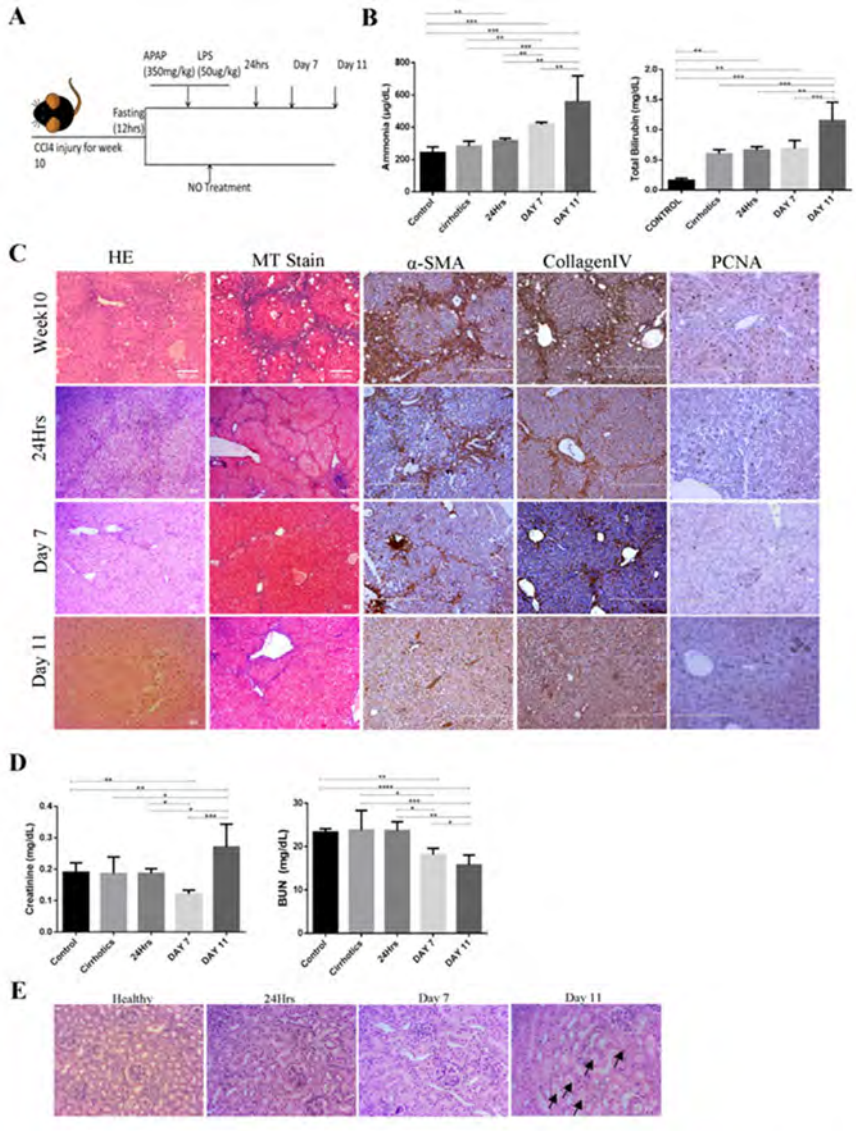

Figure 1 (A) The diagrammatic illustration of model development. (B) Liver Function test, ammonia and total bilirubin levels. (C) Liver histology at different time interval (24Hrs, Day 7 and Day 11) and immunohistochemistry w.r.t Week 10 of chronic liver injury. (D) Kidney parameters (Creatinine and BUN). (E) Histology of kidney (arrow marking ATN at week 11)

Figure: (abstract: THU323)

observed however liver showed enhanced portal inflammation with fibrosis and cirrhosis. Hepatocytes showed eosinophilic cytoplasm with enlarged reactive nucleus with marked hepatocytes proliferation (Fig 1-C). 24 h after LPS and APAP treatment hepatocytes showed ballooning and prominent peripheral condensation of organelles that gave rigid appearance to cell membrane (Fig 1). From 24 h to day 11, hepatocyte ballooning decreased with increased hepatocyte necrosis and cholestasis (figure 1-C). All animals developed ascites at day-9–11 post LPS and APAP treatment. Animals sacrificed on day 11 showed AF with SAAG 1.2 ± 0.1 g/DL. There was progressive decrease in fibrosis after APAP+LPS treatment (Figure1-C) hepatocyte proliferation markedly decrease and there was progressive increase in plasma T.bilirubin and ammonia (Fig 1B). Analysis of lungs, kidney and spleen tissue showed the presence of progressing acute tubular necrosis (ATN) from day 7 to day 11 post-acute insult with increase in serum creatinine and decrease in blood urea nitrogen (BUN) (Fig 1-E) suggesting renal injury. Interstitial pneumonia and exudate pneumonia were observed in 3 mice at day 11. Altogether these data suggested the secondary organ failure following the liver failure post APAP+LPS treatment.

Conclusion: Our model showed progressive increase in bilirubin and ammonia, ascites and secondary organ failure a characteristic feature of ACLF as per APASL/EASL and can be used to understand the pathomechanism of ACLF as well as for preclinical studies and development of new therapies.

THU324

The method of spheroid formation for 3D cultures of primary hepatocytes influences hepatocellular functions and hepatotoxicity

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Background and Aims: Primary hepatocytes of human and animal origin are the gold standard for all pharmacological-toxicological studies in drug development. They play a major role in eco-toxicological evaluation as well. Three-dimensional (3D) cultures became more popular in recent years since they might mimic the *in-vivo* cell morphology, polarity and cell-cell interactions better than traditional two-dimensional (2D) cultures. Here, two types of cell culture plates were used to generate 3D cultures with primary hepatocytes: the GravityPLUS Hanging Drop System with subsequent culture in Gravity TRAP plates in comparison to U-bottom ULA (ultra-low attachment) plates with cell repellent surfaces. Standard 2D cultures were performed as well.

Method: Hepatocellular detoxification functions like urea release and CYP450 activity as well as the response to the hepatotoxin Diclofenac were analysed in these culture systems. The results were normalized to the corresponding volume of culture medium or to protein content.

Results: The secretion of urea was improved and maintained at higher levels in U-bottom ULA plates compared to the Hanging Drop System. CYP1A activity was better inducible by beta-Naphthoflavone in U-bottom plates than in the Hanging Drop System at all 3 tested cell numbers. Basal Cytochrome P450 activities were higher in U-bottom plates and showed a better inducibility in these plates compared to the Gravity TRAP plates.

Diclofenac, a known and well-described hepatotoxic compound, did show similar effects on hepatocytes with regard to the ATP content in both 3D culture systems. Beside this, the decrease of ATP content due to Diclofenac treatment was higher in 2D culture than in the 3D culture systems.

Conclusion: In summary, our results indicate that major differences may exist between different 3D culture systems and in comparison, to standard 2D culture methods. These differences may lead to different and conflicting results in the assessment of drug toxicity and drug-drug interaction.

THU325

Bioengineering of 3D bile ducts from 2D micropatterns by self-organogenesis

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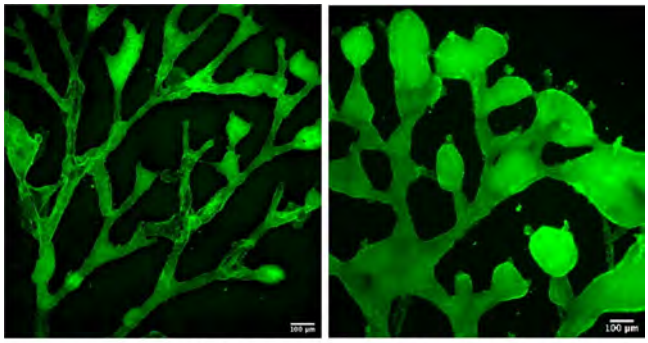
Background and Aims: Despite its central role in detoxification, a functional bile duct system has been precluded from most bioengineered liver projects. In this work, we explored the conditions allowing the development of tubular networks based on cholangiocyte self-organogenesis.

Method: Cholangiocytes were first grown as an epithelial sheet on 2D micropatterned surfaces from which tubular structures were formed by addition of hydrogels that induce self-organogenesis. Various geometries of lines and tree patterns were explored to characterize the conditions that allow the development of hollow tubes, and that favor the coalescence of lumen in the network. Polarity and secretion properties of the tubes were assessed by fluorescein secretion assays and immunolocalization of epithelial markers.

Results: By varying the geometries, sizes of the micropatterns and the source of cells, we identified conditions that allow the development of a network of bile ducts with diameters ranging from 15 to 150 µm, mimicking the organization of an intrahepatic biliary network. In particular, the co-culture with endothelial cells suggests a scaffolding effect on cholangiocyte self-organogenesis while enhancing their lumenogenesis potential to form tubes, Figure 1.

Conclusion: To our knowledge, this is the first study to present biliary duct networks built *in vitro* from 2D micropatterns inspired from the shapes of distal biliary trees. This work opens interesting opportunities for gaining insights in bile duct organogenesis and paves the way for performing functional analyses in cholangiocyte-related diseases.



Biliary duct network made from culture of biliary cells alone

Biliary duct network made from a coculture of biliary cells and endothelial cells

THU326

Histidine triad nucleotide-binding protein-2 is present at the cross-road of ER-mitochondria interactions and modulates adaptive stress response in hepatocytes

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Background and Aims: Histidine triad nucleotide-binding protein 2 (Hint-2) is a mitochondrial adenosine phosphoramidase expressed in hepatocytes. Hint2 knockout (*Hint2*$^{-/-}$) mice show hepatic steatosis, lysine hyperacetylation and reduced mitochondrial respiration, but the mechanism is unclear. Dysfunction in mitochondria affects communication with the endoplasmic reticulum (ER) via mitochondria-associated membranes (MAMs), which is mediated by associations between IP3R, GRP75 and VDAC1. Since Hint-2 itself binds to GRP75, we postulated that Hint2 modulates proteomic composition of MAMs and participates in the adaptive response of hepatocytes to ER stress.
Method: MAMs were isolated from *Hint2*$^{+/+}$ and *Hint2*$^{-/-}$ livers and subjected to LCMS/MS proteomics. Response to the ER stressor tunicamycin was tested in *Hint2*$^{+/+}$ and *Hint2*$^{-/-}$ hepatocytes and in control and Hint-2 overexpressing SNU-449 cells. Response to ethanol was examined in *Hint2*$^{+/+}$ and *Hint2*$^{-/-}$ hepatocytes and *in vivo*. Oxygen consumption rates (OCR) was assessed by XF-Seahorse analyzer.
Results: Proteomic heterogeneity was reduced in Hint2$^{-/-}$ MAMs: 113 unique proteins and 15 unique proteins were detected in *Hint2*$^{+/+}$ and *Hint2*$^{-/-}$ livers, respectively. Hint-2 itself was detected in MAMs. With tunicamycin treatment, the ER stress proteins, CHOP, XBP-1s and ATF6 increased by 53-, 22- and 11-fold, respectively, in Hint-2 overexpressing cells but only 16-, 9- and 4-fold, respectively, in control SNU-449. Similarly, CHOP increased 40-fold in *Hint2*$^{+/+}$ hepatocytes but only 13-fold in *Hint2*$^{-/-}$.
Ethanol triggered a 3.4 fold higher increase in lysine acetylation in *Hint2*$^{-/-}$ hepatocytes than in *Hint2*$^{+/+}$ ($p < 0.05$). However, the ethanol triggered ROS production was lower in *Hint2*$^{-/-}$ than in *Hint2*$^{+/+}$ hepatocytes ($p < 0.001$). As expected, basal and maximal OCRs were lower in *Hint2*$^{-/-}$ hepatocytes and further reduced after ethanol treatment ($p < 0.05$). Autophagy was triggered in ethanol treated *Hint2*$^{+/+}$ hepatocytes but not in *Hint2*$^{-/-}$. The phosphorylation (S-228) of PTEN-induced kinase 1, a marker for stress-induced mitochondrial dysfunction, was increased 2-fold only in *Hint2*$^{+/+}$ mitochondria.
Conclusion: Hint2, a mitochondrial protein, partly resides in MAMs and its absence changes the proteomic landscape of MAMs. Lack of Hint2 diminishes cellular sensitivity to tunicamycin and ethanol-mediated ER stress. Therefore, we conclude that Hint2 participates in the adaptive response of hepatocytes to ER stress.

THU327

Analysis of HBV full-genome haplotypes from immune tolerant-, immune clearance-, and immune resolution phase of chronic hepatitis B virus disease

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Background and Aims: The absence of proof-reading in the reverse transcriptase during Hepatitis B virus (HBV) replication generates haplotypes, which may emerge depending on selection pressure and viral fitness in chronic hepatitis B (CHB) disease.
Method: We investigated haplotype frequency and diversity at both the nucleotide and amino acid level across the complete HBV genome in 4110 haplotypes from 368 patients with history of CHB during three phases of natural history of disease, immune tolerant, immune clearance, and immune reactivation, for genotypes A to D. Haplotype frequencies were compared to serum HBsAg, HBeAg, HBV DNA viral load, and liver alanine aminotransferase.
Results: Number of haplotypes per samples (frequency) was higher in samples from patients of Asian ethnicity (genotype B and C) compared to Caucasians (genotype A and D), and in the immune clearance and immune reactivation phase compared to immune tolerant phase. Haplotype frequencies and genetic diversity increased over the course of CHB history, from the immune tolerant, to the immune clearance and immune reactivation phases for most genotypes, except for genotype C. Haplotype genetic diversity varied across CHB natural history, most notably in the precore/core gene. Analysis of sequence conservation across all five functional genes and all six regulatory regions in all 4110 haplotypes showed that between 18.2% and 41.8% of nucleotides and between 5.9% and 34.3% of amino acids in the HBV genome were 100% conserved, depending on the genes and regions analysed. Haplotype frequencies were generally negatively correlated with HBsAg titre, HBeAg titre and viral load, although this varied by HBV genotype and CHB. The highest negative correlation was observed between genotype A immune clearance samples and HBsAg titre (Spearman R –0.7292, P < 0.0001) and HBeAg titre (Spearman R – 0.7383, P < 0.0001) and between genotype D immune clearance samples and HBsAg titre (Spearman R – 0.5513, P 0.0002) and HBeAg titre (Spearman R – 0.5801, P = <0.0001).
Conclusion: These findings reveal a previously unrecognised degree of HBV haplotype heterogeneity across the complete HBV genome, which spans multiple phases of CHB natural history. Highly conserved sequences were identified at both the nucleotide and amino acid level in key genes and regulatory regions, which may be suitable targets for antiviral therapies.

THU328

Tolerogenic dendritic cells modulate pathogenic CD4+ T cells in an ex vivo co-culture system in a concanavalin A -mice model of type-I autoimmune hepatitis

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Background and Aims: Tolerogenic dendritic cells (tolDCs) have the potential to prevent autoimmune hepatitis via sustained release of immunoregulatory cytokines, increased induction of regulatory T cells and suppression of autoreactive/effector T cells. In the present study, we investigated the modulation of pathogenic CD4$^+$ and CD8$^+$ T cells by syngenic tolerogenic DCs.
Method: Tolerogenic dendritic cells were generated from mouse bone marrow using immunoregulatory IL-10. Phenotypic and functional characterization of induced DCs was done by flowcytometry. Gene expression for inflammatory and maturation markers was estimated via RT-PCR. Syngenic tolerogenic DCs were co-cultured with liver pathogenic CD4$^+$ and CD8$^+$ T cells, derived from mice mode of autoimmune hepatitis, *ex* vivo to observe modulation of CD24, TIM-1 and TIM-3 molecules.
Results: Ex vivo generated tolDC had an adherent phenotype with low surface expression of CD80, CD86, CD40, MHC-II and relatively high surface expression of PD-L1 and PD-L2. The tolDCs had poor CD4$^+$ T cell stimulatory capacity and also showed greater Treg induction potential. Tolerogenic DCs had high mRNA expression of TGFβ1, PD-L1 and low expression of CCR7, IL-12. In the co-culture study, tolerogenic DCs were found to downregulate CD24 and upregulate TIM-3 on T cells.
Conclusion: This study is first of its kind to demonstrate immunomodulation of pathogenic T cells by tolerogenic dendritic cells. Based on our results, we found that tolerogenic DCs could not only suppress

proliferation of IFNγ secreting effector cells but also promote additional immunological regulation via increasing expression of inhibitory TIM-3 molecule. We strongly suggest that a therapy involving tolDCs can effectively inhibit acute or chronic inflammation leading to autoimmunity.

THU329

Hepatic inflammation upregulates netrin-1 in mice and in vitro through translational activation and transcript topology alteration in a LA-related protein-1 (LARP1)-dependent manner

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Background and Aims: Links between hepatic inflammation and HCC are likely incompletely defined. Netrin-1 is a developmental neurogenic factor reactivated upon general carcinogenesis and bearing pro-tumorigenic properties (Mehlen, Nat. Rev. Cancer 2011). Converging data indirectly suggest its detrimental implication in end stage liver pathology, including HCC (Plissonnier et al. Plos Biol 2016 & Oncogene 2017; Lahlali et al. CMGH 2016).
Method: In the present study, patient samples, mouse samples as well as in vitro cell biology and mechanistic approaches were used.
Results: We show that netrin-1 mRNA (*NTN1*) levels positively correlated with activity scores of human livers biopsies (up to +6-fold in A2 vs A0 samples, p = 0.02, n = 162, Panel A). Using poly(I:C) as a TLR3 agonist, experimentally-induced inflammation in mice upregulated netrin-1, through the implication of parenchymal cells (Panel B). Netrin-1 was found in vitro-inducible by a panel of TLR2 to 6 agonists, a dataset strengthening the pathophysiological relevance of this in vitro phenotype (Panel C). Surprisingly, neither total mRNA levels (RT-qPCR), nor transcriptional levels (plasmid reporter assays, pre-mRNA RT-qPCR) nor splicing (mRNA over pre-mRNA ratios calculations), nor mRNA stability were found implicated (not shown). In contrast, robust transfer of *NTN1* to the ER (+7-fold, p < 0.05, as observed by sequential fractionation) and its translational activation could be evidenced (+40%, p < 0.05, by polysomal fractionation as well as polysomal run-off on HepaRG cells and PHH, respectively, Panel D). This phenotype was reversed by RNAi depletion of the La Related Protein-1 (LARP1) RNA binding protein (Panel E). This dataset suggests phenotypical convergence for netrin-1 induction through distinct regulatory scenarios depending on the cellular context (HepaRG or PHH). Secretory levels of the hepatocyte-like cells were left unchanged (AAT-GFP RUSH assay), suggesting the non-implication of netrin-1 secretion alteration in this phenotype.
Conclusion: Such data identify the less frequently addressed polysomal activation and mRNA topological regulation processes as sufficient events allowing netrin-1 induction. They also further document the pathogenic consequences of inflammation in the liver, in the present case through the implication of netrin-1, a documented carcinogenic factor.

THU330

Cirrhotic extracellular matrix affects Hic-5 expression in primary human hepatic stellate cells

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Background and Aims: Activation of hepatic stellate cells (HSC) by transforming growth factor beta (TGFb) is a well-established driver of liver fibrogenesis. Previously we demonstrated that primary human HSC (hHSC) cultured in a 3D model based on human liver extracellular matrix (ECM) scaffolds, showed a different cell behaviour compared to the traditional 2D plastic cultures. In this study we aim to assess the impact of the liver ECM environment (healthy versus fibrotic) on the expression of a TGFb1-modulated protein, namely Hydrogen peroxide Inducible Clone-5 (HIC-5), in primary hHSC cultured in decellularized healthy and cirrhotic human liver ECM scaffolds.

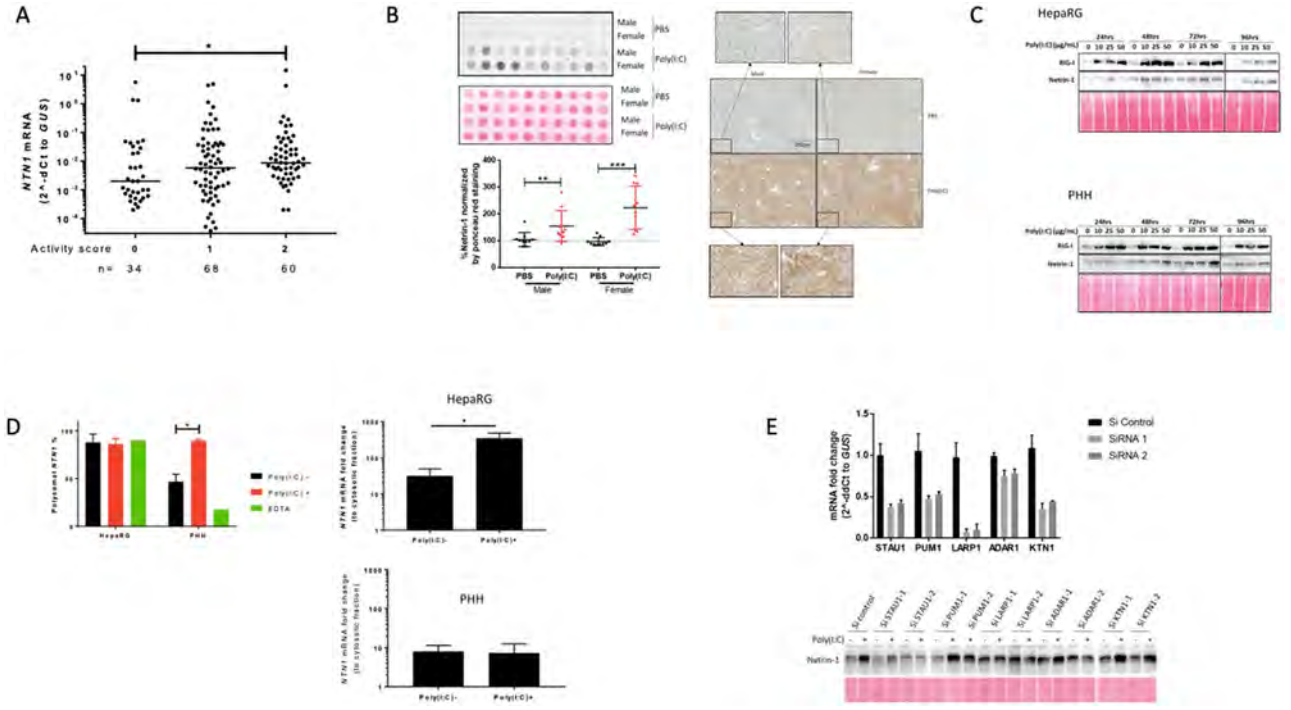

Figure: (abstract: THU329)

Method: Decellularized human liver 3D scaffolds were repopulated with primary hHSC ($0.25*10^6$) for 10 days. HSC were exposed to H_2O_2 (100 uM) and TGFb1 (5 ng/mL) for 24 h, w/wo pre-treatment of H_2O_2/TGFb1. HSC engraftment was assessed histologically and by immunohistochemistry, while viability was quantified by PrestoBlue assay. Pro-fibrogenic protein expression was assessed by Western Blot.
Results: Engraftment in healthy and cirrhotic scaffolds was demonstrated histologically, while Prestoblue assay showed that hHSC remain viable in both types of scaffolds.
Simultaneous exposure to H_2O_2 and TGFb, pretreatment with H_2O_2 followed by TGFb, or TGFb pretreatment followed by H_2O_2 exposure upregulated HIC-5 protein expression in HSC engrafted in cirrhotic scaffolds compared to healthy scaffolds. This finding indicates that TGFb and H_2O_2 affect HIC-5 regulation and hHSC activation when cultured in diseased ECM scaffolds. A similar tendency was observed in Acta2 protein expression which showed to be highly upregulated in all conditions tested in cirrhotic scaffolds compared to healthy scaffolds, further demonstrating the strong impact of fibrotic ECM on hHSC behaviour.
Conclusion: Primary hHSC express differently HIC-5, when cultured in healthy versus cirrhotic 3D ECM scaffolds suggesting that their activation status and response to fibrogenic stimuli is strongly affected by the hepatic ECM features. These findings support the use of human tissue-specific 3D scaffolds as a more realistic pathophysiological model to further investigate the role of HIC-5 in primary hHSC and to define the specific role and modulation of the TGFb1 signalling pathway in hepatic fibrogenesis.

THU331

Phenotypic characterization of ABCG5/G8 deficiency: selective knockout in liver or intestine leads to genocopies

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Background and Aims: Gallstone disease is one of the most common disorders worldwide. Gallstones result from cholesterol supersaturation of bile, which causes the formation of cholesterol crystals in hypomotile gallbladders. Cholesterol is transported across the hepatocanalicular membrane by the heterodimeric ATP-dependent transporter ABCG5/G8. Besides its function in the liver, *Abcg5/g8* is also expressed in the intestine. The specific aim of this study was to compare the physical-chemistry of bile secretion and gene regulation when the transporter is selectively disrupted in liver or intestine, respectively.
Methods: Using BAC-based recombineering, we have generated conditional *Abcg5/g8* knock-out mice allowing tissue-specific deletion of the first two exons of *Abcg5* and the first exon of *Abcg8*, respectively, by Cre-mediated recombination. *Abcg5/g8* flox mice were crossed to *Villin*-Cre mice, expressing Cre in the intestine under the control of the *Villin* promoter (Int-KO), and *Albumin*-Cre mice, allowing hepatocyte-specific deletion of the transporter (Hep-KO). Hepatic bile was obtained after cannulation of the common bile duct, and bile flow and biliary lipid secretion rates were measured during the first three hours of the acute bile fistula. In addition, lipid and expression analyses of cholesterol regulatory genes in liver and intestine were performed.
Results: Conditional knockout mice developed normal, were fertile, and showed no gross abnormalities. Int-KO mice presented with higher liver to body weight ratios as compared to Hep-KO mice, whereas body and liver weights did not differ. Bile acid concentrations were elevated in bile of Int-KO mice, and phospholipids were decreased. Cholesterol and cholesterol saturation indices (CSI) were higher in conditional knockout mice (CSI = 2.1–2.3), but did not differ between Hep-KO and Int-KO. Hepatic cholesterol concentration were similar, but phytosterols accumulated massively in the livers from both conditional knockout strains (wild-type: 17.4 ± 4.6, Hep-KO: 199.4 ± 86.1, Int-KO: 494.9 ± 611.3 mg/g cholesterol; p = 0.002). The expression of the alternative cholesterol transporter *Abcg1* as well as the bile acid transporter *Abcb11* were decreased in livers of Int-KO mice, while *Fxr* expression was increased. The expression pattern of *Hmgcr, Cyp7a1, Acat1, Srebf1/2, Ldlr* and *Npc1l1* was comparable between genotypes.
Conclusions: Our results illustrate that the tissue-specific deletion of *Abcg5/g8* in either liver or intestine leads to comparable phenotypes (genocopies) regarding biliary lipid output and expression of cholesterol metabolism-related genes. Expression of the transporter at both sites appears critical and exerts synergistic effects to maintain sterol balance in liver and bile.

THU332

Synthesis and comparative assessment of bile acid C3-hydroxyl stereoisomers as farnesoid X receptor modulators

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Background and Aims: Primary bile acids (BAs) are synthesized from cholesterol in the liver and usually occur with a C-3 hydroxyl group in alpha configuration (3a-OH). The binding of BAs by the farnesoid X receptor (FXR) is crucial in the regulation of hepatic and intestinal steroid- and lipid homeostasis. Microbial metabolism produces secondary BAs and stereoisomers with C-3 hydroxylation in beta configuration (3b-OH, isoBAs), the latter being re-epimerized to their 3a-OH forms in rat and human livers. To gain further insights into the physiologic and regulatory functions of 3b-OH BAs, we investigated a series of different BA-stereoisomers on FXR activation using cultured cells and C57/BL6 mice.
Method: Individual isoBAs, in comparison to their 3-alpha stereoisomers were tested for FXR transactivation using a) RNA expression profiling of cultured cells, b) luciferase-based assays, c) fluorescence-based coactivator association assay (BA-Sensor) that measure FXR activation in real time, and d) in vivo, by administering C57/BL6 mice with various isoBAs at (50 mg/kg).
Results: We first show that isoBAs are less toxic to cultured cells than their 3a-OH isomers (100 µM vs. vehicle). HepG2 cells were treated for 16 h with chenodeoxycholic (CDCA), deoxycholic (DCA), or ursodeoxycholic (UDCA), and their 3b-stereoisomers and FXR target genes were quantified by Q-PCR. CDCA and isoCDCA strongly activated FXR; DCA and isoDCA weakly increased, whereas UDCA and isoUDCA were virtually inactive on mRNA levels of FXR target genes. However, all BAs increased the precursor-mRNA (pre-mRNA) of FXR target genes (CDCA>DCA>UDCA). The regulation of target genes (ratio pre-mRNA/mRNA) seems to depend on the localization of mRNA and its half-life (e.g. *Kng*1, nuclear; long half-life; *Ost*-b cytosolic, short half-life). Importantly, we further realized that already after 4–5 h 50% of isoBAs were metabolized to 3-oxo BAs (inactive for FXR) making it difficult to study the full impact on FXR activity or to compare to 3a-isomers in cell based assays with long treatment duration. Real time monitoring of FXR activity using the BA-senor revealed that i) isoCDCA > CDCA activated FXR, and iso-DCA/UDCA were ineffective; ii) iso-DCA/UDCA suppressed FXR activation by CDCA; iii) fully activated FXR (saturated), cannot be further stimulated even by highly potent FXR agonists (e.g. GW4064). Importantly, iso-DCA/UDCA allowed saturated FXR to be re-activated by GW4064. In mice, co-administration of a single dose of iso-DCA/

UDCA slightly potentiated the effect of GW4064 on repression of *Cyp*7a1 or induction of FXR targets in liver and intestine.
Conclusion: A burst induction and a short half-life of target gene mRNA are needed to observe proper FXR activation. Secondary (iso)-BAs allow reactivation of saturated FXR that would assure cycling dynamics and accurate control of gene transcription within the enterohepatic circulation.

THU333
Upregulation of CCNB1, CDC20 and CENPF genes is associated with poor prognosis in hepatocellular carcinoma (HCC)
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Background and Aims: Hepatocellular carcinoma (HCC) is the most common primary liver cancer with a low 5-year survival rate. The early stage of HCC is usually asymptomatic and many patients were diagnosed at the late stage and missed best chance to be treated effectively. Screening or surveillance with ultrasound in conjunction with alpha fetoprotein (AFP) is inefficient in detecting early tumour; therefore, new and sensitive biological markers for disease are required. The aim of this study was to search for potential gene markers for the early identification of HCC.
Method: Four GSE profiles (GSE6764, GSE6222, GSE101685 and GSE102083) were screened out after searching the GEO database. Candidate genes with at least a 2-fold change (|log FC|>2) in expression were filtered using Venn diagram software. Core genes from the protein-protein interaction (PPI) network were identified through online dataset STRING and Cytoscape software (MCODE module analysis). The correlation between the core genes and prognosis of HCC was sought. The biologically functional contributions of poor-prognosis related genes were recognised via GO and KEGG enrichment analysis. The diagnostic and predictive values of the identified genes were also verified by the GEPIA and HPA database.
Results: A total of 202 common differentially expressed genes (52 up-regulated and 150 down-regulated) were filtered from the GSE profiles (Figure 1A). 32 genes were potentially associated with poor prognosis of HCC (Figure 1B), of which 12 were found to be significantly up-regulated in HCC tumour tissue (Figure 1C). Analysis of the 12 core genes by GO and KEGG enrichment analysis revealed that CCNB1, CDC20 and CENPF were involved in the development of HCC. Positive correlations among these three genes were identified and all signatures of three genes were associated with worse prognosis of HCC (Figure 1D & E). The PCA analysis indicated that these three genes could clearly distinguish HCC tumour tissue from normal liver tissue (Figure 1F & G). Moreover, among digestive tract tumours, CCNB1, CDC20 and CENPF were uniquely associated with significant survival difference in HCC (Figure 1F).
Conclusion: CCNB1, CDC20 and CENPF genes were identified to associate with HCC poor prognosis. The expression of these genes might serve as sensitive biomarkers for the early diagnosis of HCC.

THU334
Bax inhibitor-1 inhibits acetaminophen induced hepatotoxicity by reducing the drug induced ER stress through regulating the RIDD activity of IRE1 alpha
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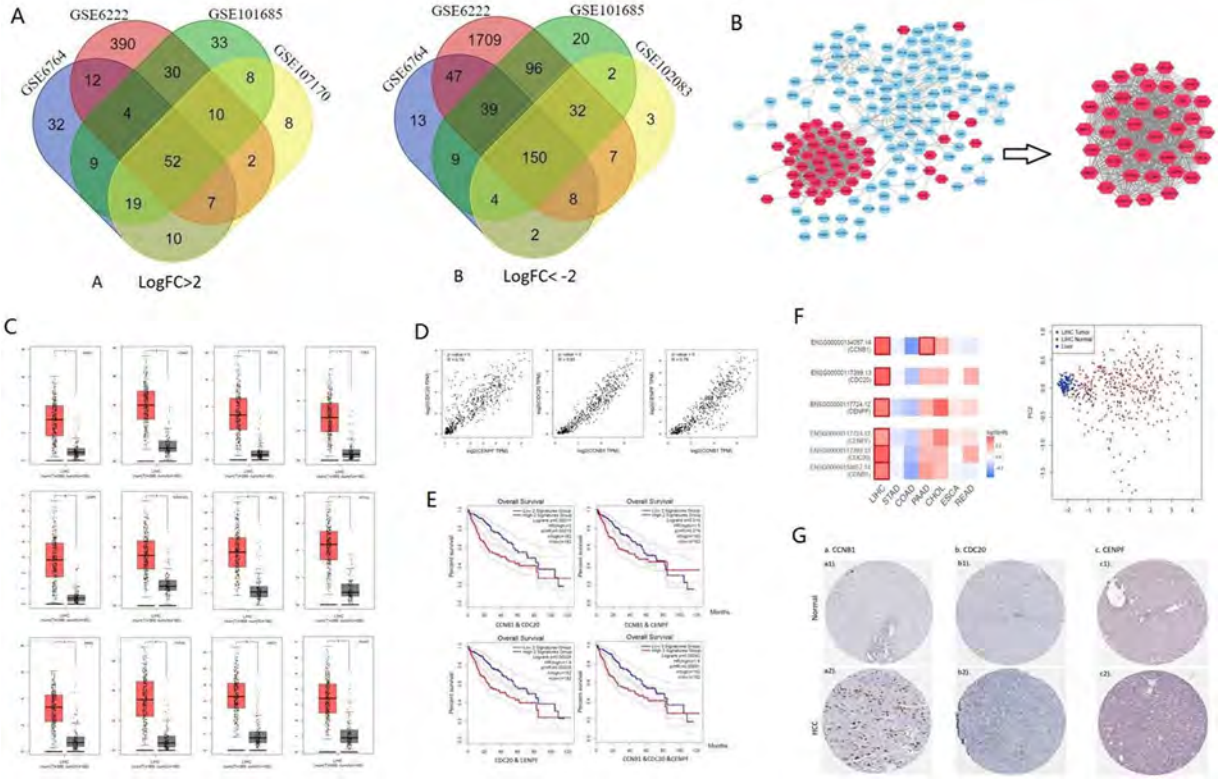

Figure: (abstract: THU333)

POSTER PRESENTATIONS

Background: Acetaminophen (APAP) overdose is the most frequent cause of acute liver failure and is primarily caused by CYP2E1 driven conversion of APAP into NAPQI, a hepatotoxic metabolite. APAP induced oxidative stress creates intraluminal redox imbalance of the ER and consequential activation of UPR and proapoptotic signaling. Bax inhibitor1 (BI-1),an antiapoptotic protein known to suppress the cell death by regulating ER stress response.

Aims: To study, whether BI-1 gives the protective effect against APAP induced ER stress. If so, to find out the possible mechanism of BI-1 which give the protective effect.

Method: Hep3B cell line overexpressing BI-1 and Neo were cultured in DMEM medium supplemented with 10% FBS and 100 μg/ml streptomycin, and 100 units/ml penicillin. Acetaminophen treated at 10 mM concentration and cells were harvested at 0, 3, 6, 12, and 24 hours after treatment. BI-1 wild type and BI-1 knockout mice of 9 weeks old were treated with APAP, 500 mg/Kg body weight for 24 hrs. Samples were examined for the immunoblot and histology.

Results: Our results showed that APAP induced ER stress was reduced in the presence of BI-1 and BI-1 over expressing cells compare knockout and neo control system respectively. BI-1 knockout mice showed massive hepatotoxicity and large number of cytoplasmic vacuoles as revealed by H&E staining. Further it increased ALT and AST levels, protein oxidation and lipid peroxidation. We observed reduction of CYP2E1, a RIDD substrate, expression in BI-1 over-expressing cells. To examine the possible relation of BI-1 in CYP2E1 lower expression in the ER stress, we hypothesized that BI-1 may regulate the IRE1 response. As, it is known that XBP1s requires oligomer sate of activated IRE1α and this XBP1s is reduced in BI-1 expressing cells but at the same time phosphorylation of IRE1 was also observed. So, It indicates that in BI-1 overexpressing cells IRE1α is activated but held in dimer state for extended time compare to PC cells. In consequence, the dimer state of activated IRE1α has the RIDD activity and helps in initial adaptive stress response by reducing the further load of protein synthesis during ER stress. As a consequence CYP2E1 mRNA degraded and resultantly lesser conversion of APAP to toxic metabolite. So, our results suggest a role for BI-1 in the regulation of RIDD activity in early adaptive responses against APAP induced ER stress.

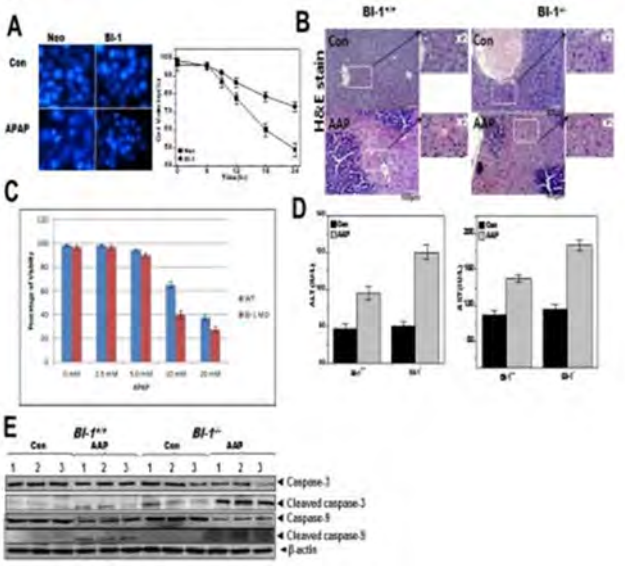

Fig. 1. BI-1 reduced the acetaminophen induced cell apoptosis and liver injury in mice.

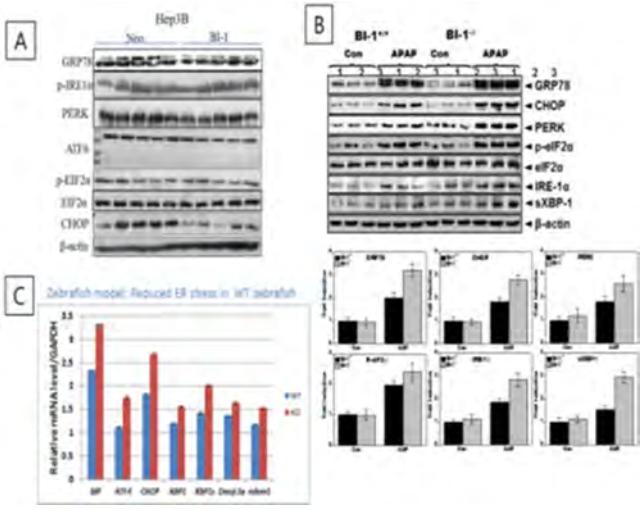

Fig. 2. BI-1 reduced the acetaminophen induced ER stress.

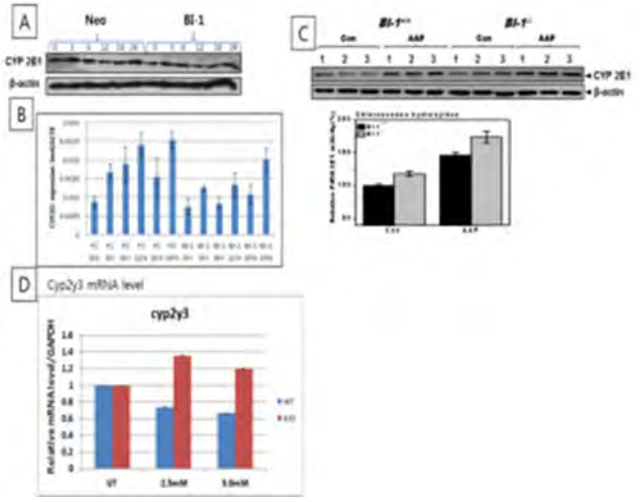

Fig. 3. CYP2E1 expression is reduced in presence of BI-1.

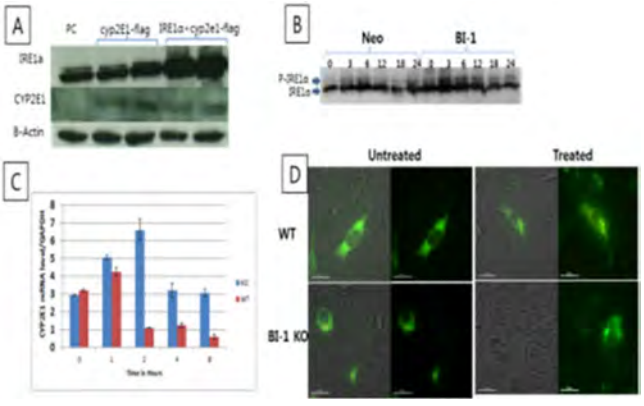

Fig. 4. BI-1 reduces oligomerization of IRE1α.

Conclusion: Phosphorylation of IRE1α was observed but not oligomerization in the presence of BI-1,CYP2E1 mRNA levels were reduced in the presence of BI-1 and resulted in less toxic effect of APAP. Further, experiments need to be carried out to fully confirm the BI-1regulation of IRE1α.

THU335

Circular RNA circ-TEX2 acts as the sponge of miR-182 and miR-184 to suppress hepatocellular carcinoma proliferation and invasion

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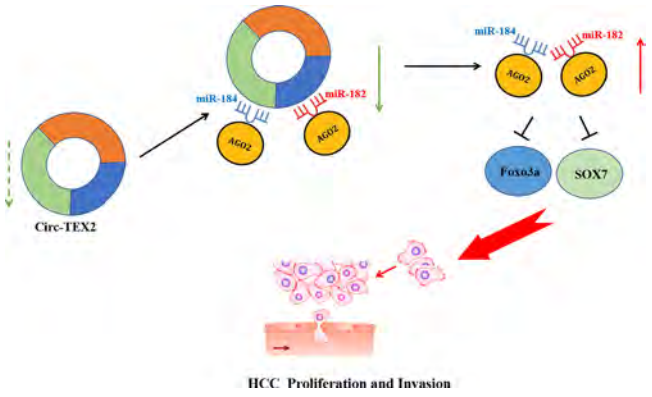
Background and Aims: Multiple circular RNAs are dysregulated in Hepatocellular carcinoma (HCC). However, the function and molecular mechanism of them are largely unclear. Previous studies suggested that circular RNAs can play important roles in the development of cancer. Therefore, identify the key circular RNAs in HCC and reveal their potential function and molecular mechanism have important significance for improving the diagnosis and treatment of HCC.
Method: The dysregulated circular RNAs were identified through integrating the analysis of three human circular RNA microarrays (GSE94508, GSE97332 and GSE 78520) and were further validated using qRT-PCR in HCC tissues and HCC cell lines. The characteristics of circular RNA were verified through Sanger sequencing, divergent primer PCR, RNase R treatment, RNA intracellular localization analysis and the structure was predicted in Mfold. The functions of circular RNA in HCC were assessed through CCK8 assays, clone formation assays, EDU assays and Transwell assays in vitro and tumor xenografts in vivo. The mechanism of circular RNA in HCC was demonstrated using dual-luciferase reporter, RNA immunoprecipitation assays and western blot.
Results: Circ-TEX2 was down-regulated in HCC and associated with the pathological staging of HCC. The vitro experiments showed that overexpressing circ-TEX2 can significantly inhibit the proliferation and invasion of HCC cells. Tumor xenografts in vivo also confirmed that circ-TEX2 can effectively suppress the growth of HCC. Furthermore, we demonstrated that circ-TEX2 can bind with miR-182 and miR-184 to up-regulate the expression of their downstream target genes (Foxo3a and SOX7).



Conclusion: Our study reveal that the down-regulation of circ-TEX2 in HCC attenuates the binding of circ-TEX2 and miR-182 or miR-184 to release their functions which decrease the expression of Foxo3a, and SOX7, ultimately enhance the proliferation and invasion of HCC.

THU336

CircRNA_104797 mediates acquired sorafenib resistance in hepatocellular carcinoma through regulating ROS

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Background and Aims: Hepatocellular carcinoma (HCC) is a fatal cancer with limited treatment methods. Sorafenib is one offering great clinic benefit. However, sorafenib resistance often occurs within one year. The mechanism behind sorafenib resistance is still unclear. Circular RNAs (circRNAs) are widely expressed noncoding RNAs with complicated biological functions. Recently, some studies found that circRNAs may play important roles in regulating reactive oxygen species (ROS) and mediate drug response. In this study, we aimed to study circRNA_104797 in regulating sorafenib response through ROS regulation.
Method: Sorafenib resistant (SR) cell lines were established by sustained treatment of small dose of sorafenib in the media. A CircRNA Array analysis and mass spectrum were carried out to detect possible targets. Flow cytometry was performed to analyze ROS and apoptosis level. Protein level was measured by western blotting. RNA pulldown and immunoprecipitation were carried out to detect possible binding between circRNA and protein. Confocal fluorescence microscope was used to reveal colocalization between circRNA and protein.
Results: In this study, we found a circRNA named circRNA_104797 was upregulated in HepG2 SR cell line compared with parental cell. Depletion of circRNA_104797 by siRNA transfection could increase cellular ROS and induce mitophagy; while overexpression of circRNA_104797 could reduce ROS level under sorafenib treatment. Besides, we found the ROS scavenger N-acetyl-cysteine could reduce apoptosis level induced by circRNA depletion. Mass spectrum analysis was performed to explore distinctive proteins after circRNA depletion. Another mass-spectrometry was conducted to analyze protein binding with this circRNA. Results suggested protein Ubiquilin 1 was stabilized by circRNA_104797. RNA immunoprecipitation, RNA pulldown and confocal fluorescence microscopy results confirmed our suggestion. What's more, Ubiquilin 1 degradation was accelerated after circRNA_104797 depletion. Overexpression of Ubiquilin 1 could partly reduce apoptosis caused by circRNA depletion.
Conclusion: Our results uncovered one function mechanism of circRNA_104797. Under sorafenib treatment, circRNA_104797 mediated ROS regulation through stabilizing Ubiquilin 1. Therefore, circRNA_104797 and Ubiquilin 1 may offer to be potential targets in treating HCC.

THU337

Ubiquilin 1 mediates sorafenib resistance in hepatocellular carcinoma through targeting mitochondrial biogenesis via regulating PGC1?

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Background and Aims: Hepatocellular carcinoma (HCC) is a fatal cancer with limited treatment options. Systemic treatment using sorafenib offers great clinical curativeness; however, resistance often occurs. The mechanisms of resistance include dysregulation of PI3K/Akt and JAK/STAT pathways, epithelial–mesenchymal transition, and the hypoxia-inducible response. Meanwhile, recent studies have revealed sorafenib targets electron transport chain complexes, resulting in reactive oxygen species (ROS) generation. This study aimed to study the role of ROS in sorafenib resistance.
Method: Flow cytometry was used to measure intracellular ROS levels. Oxygen consumption rate (OCR) detection and transmission

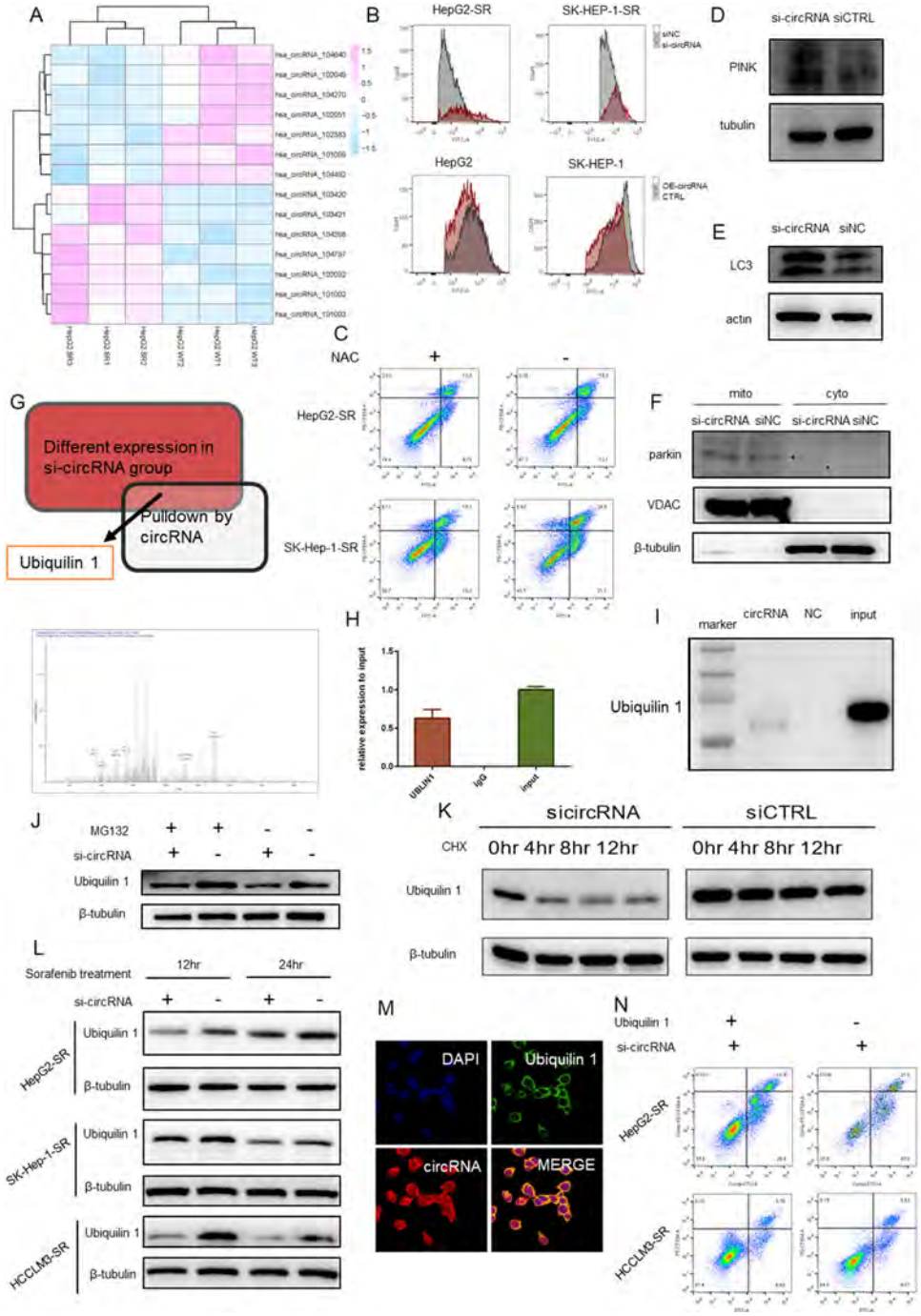
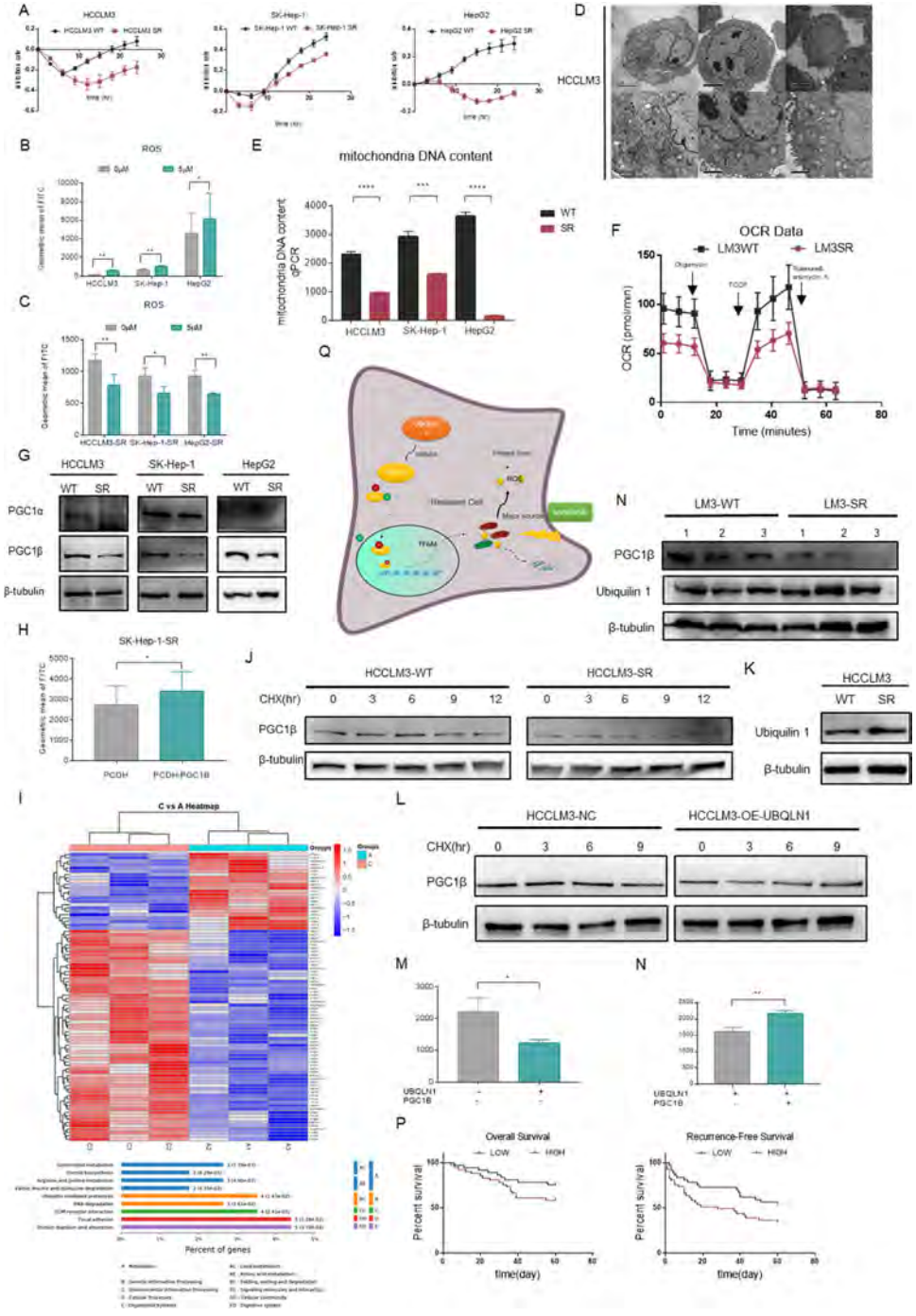


Figure: (abstract: THU336)

electron microscopy were adopted to investigate the function and morphological changes of mitochondria. Western blotting and qRT-PCR were used to measure protein and mRNA levels. A mass spectrum was performed to identify distinctive proteins. Expression level of ubiquilin 1 in patient tissue was valued by immunohistochemistry.

Results: Sorafenib induced ROS responses were repressed in sorafenib-resistant cells than parental cells. Mitochondria maintained greater integrity both functionally and morphologically in resistant cells under sorafenib treatment. However, the number of mitochondria decreased in sorafenib-resistant cells, as detected via transmission electron microscopy, mitochondria DNA content and cellular OCR measurements. Further investigation found mitochondrial biogenesis was inhibited by downregulated expression of peroxisome proliferator-activated receptor γ coactivator 1β (PGC1β). In addition, we found that ubiquilin 1 was upregulated in sorafenib-resistant cells, and thus accelerates the protein degradation of PGC1β to attenuate ROS generation under sorafenib treatment in sorafenib-resistant cells. Importantly, genome wide proteome analysis with mass-spectrometry between the parental and sorafenib-resistant HCC tumors from mouse models showed that proteins altered in sorafenib-resistant cells were enriched in ubiquitin-mediated proteolysis pathway and mitochondrial organization function. Clinical data further demonstrated that patients with high ubiquilin 1 levels had worse recurrence-free survival.



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Conclusion: We proposed a new mechanism of sorafenib resistance in relation to mitochondrial biogenesis and ROS generation. We found that upregulation of Ubiquilin 1 in sorafenib-resistant HCC cells enhanced the degradation of PGC1β, which resulted in down-regulated mitochondria number and suppressed ROS level, thus contributing to the sorafenib resistance. These findings provide novel mechanistic insights and therapeutic strategies for HCC patients.

THU338

Investigating the mechanism of treating acute-on-chronic liver failure with human bone marrow-derived mesenchymal stem cells via hepatocytes exosomal miRNAs

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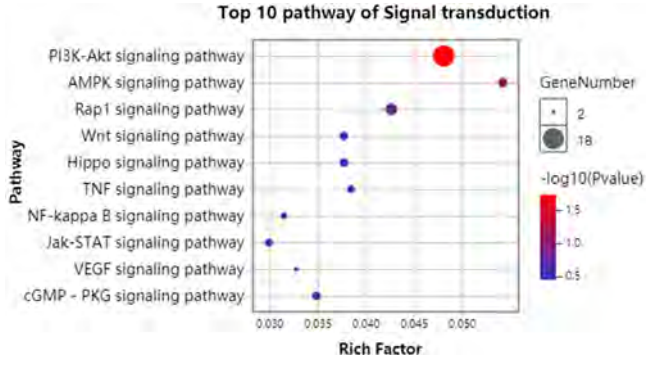
Background and Aims: Acute-on-Chronic liver failure (ACLF) is a severe syndrome of liver disease; The mortality rate is up to 30–50% in non-transplanted patients in worldwide. It is reported that human bone marrow mesenchymal stem cells (BMSCs) can improve the prognosis of ACLF, but the underlying mechanism remains unclear. To explore the roles of BMSCs on hepatocyte-to-hepatocyte communication, we used next-generation sequencing (NGS) and bioinformatics techniques to detect exosomal miRNAs in the hepatocyte microenvironment and to try to find the key genes and signaling pathways that could be affected hepatocytes survival.
Method: Primary hepatocytes from normal or ACLF mice were isolated and cultured in vitro. Human BMSCs were co-cultured with ACLF primary hepatocytes. Isolated exosomes from cell supernatant and build the miRNAs sequencing database.
The study include the normal group, the ACLF group and the BMSCs treatment group. The final target genes were analyzed by Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis.
Results: Human BMSCs could reverse the change of exosomal miRNA abundance in the hepatocyte microenvironment of ACLF mice. In the ACLF group, 44 miRNAs were down-regulated, such as miR-122-5p and miR-148a-3p. 88 miRNAs were up-regulated, such as miR-24-3p and miR-99a-5p. Accordingly, 151 genes were up-regulated and 246 genes were down-regulated in the ACLF group. GO enriched 62 differentially expressed genes related to cell proliferation. CXCL5, SOX4, IGF1, Wnt and some other genes could be the targets for promoting hepatocyte growth. KEGG enrichment annotates the pathways associated with cell growth, death, and signal transduction. The PI3K-AKT signaling pathway could be up-regulated by BMSCs in ACLF hepatocytes.



Conclusion: Human BMSCs can regulate the exosomal miRNAs of hepatocytes in ACLF, which may affect the prognosis of patients. The further study need done to confirm these results and developing new therapeutics methods for ACLF.

Viral hepatitis C: Clinical aspects except therapy

THU339

A novel hepatitis C intervention in Denmark to test and treat people who inject drugs

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Background and Aims: Providing testing and treatment for hepatitis C (HCV) for people who inject drugs (PWID) is a key component in eliminating HCV. Reaching this population with health care services can be challenging. Combining point-of-care testing with peer support and counselling has been shown to be effective. However, treatment also needs to be more accessible. The aim of this study was to investigate if a mobile van equipped with rapid detection tests for HCV antibodies and RNA could test and link PWID to care and treatment in a hospital.
Method: In Copenhagen, Denmark, a peer-led mobile service providing counselling, anti-HCV testing (In-Tech™), and linkage to standard of care was equipped with a point-of-care HCV-RNA finger-prick test (Xpert HCV Viral Load *Finger-Stick* Point-of-Care Assay, Cepheid). All clients were eligible for testing but only those with a legal residence in Denmark could be referred for treatment. Eligible HCV-RNA+ individuals were offered assisted referral to a fast-track hospital clinic for treatment, and peers provided assistance as needed.
Results: From 1 May to 31 October 2019, a total of 304 anti-HCV tests were performed, and 42 individuals were found to be HCV-RNA+. In addition, 6 individuals with known HCV infection contacted the service to be linked to care. Of the 48 individuals with possible chronic HCV infection, 24 (50%) were evaluated at the hospital clinic and by 15 November 2019, all had initiated treatment with direct-acting antiviral therapy. The main reasons for not being evaluated were being in the country illegally (n = 10, 42%) and being lost to follow up (n = 8, 33%). Two died before being linked to care and two ended up in prison. Among those initiating treatment, 14 were connected to drug treatment services and could be treated while receiving opioid substitution therapy. The peer-led service assisted all treated with inter alia communication with the hospital nurse, collecting medicine, and accompaniment to follow-up visits.
Conclusion: A peer-led mobile service can engage PWID in HCV testing and treatment. We identified being an illegal migrant as a major cause for not accessing care. This poses a challenge for HCV elimination in Denmark, in part due to the risk of onward transmission, and is a health threat to the individual.

THU341

Kidney transplant from hepatitis C positive donors to hepatitis C negative recipients: report on the first experience in the UK

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Background and Aims: Recent papers have reported the safety of transplanting kidneys from Hepatitis C (HCV) positive donors to HCV negative recipients with initiation of pan-genotypic therapy immediately after detecting transmission post-transplantation. Sustained SVR near 100% have been achieved.
Method: Cardiff Transplant Unit is the first unit in the United Kingdom to transplant kidneys from HCV positive donors into suitably consented HCV negative recipients. Details of the service development will be presented. Strong established links with virology and infectious diseases team and work in partnership with patients enabled the programme to be established. We present data from 9 kidney transplant recipients who received a transplant from 6 HCV positive donors.

No.	Age	Sex	Transplant Date	Transplant type	Date PCR positive	VL	Genotype	Treatment start date	Treatment
1	64	M	26/05/2019	DCD	05/06/2019	121176	3a	07/06/2019	Maviret
2	84	F	26/05/2019	DCD	05/06/2019	89661	3a	07/06/2019	Maviret
3	70	M	29/6/19	DBD	03/07/2019	5285	3a	05/07/2019	Epclusa
4	31	M	2/7/19	DBD	12/07/2019	104	3a	17/07/2019	Epclusa
5	33	M	02/07/19	DBD	23/07/2019	99642	TBC	23/07/2019	Epclusa
6	76	M	9/7/19	DCD	12/07/2019	24191	1a	17/07/2019	Maviret
7	70	M	24/08/19	DBD	28/08/2019	59	TBC	30/08/2019	Epclusa
8	47	M	24/08/19	DBD	30/08/2019	240	TBC	03/09/2019	Epclusa
9	37	M	14/10/2019	DBD	17/10/2019	22	1a	18/10/2019	Maviret

Figure: (abstract: THU341)

Results: Between May and September 2019, nine Caucasian patients (8 male, 1 female) in Cardiff have received kidney transplants from HCV positive donors. The mean (+/– SD) age of recipients was 55 +/– 12 years. All developed viraemia within 3 to 7 days after transplant and have been treated with pan-genotypic therapy. Four have been treated with Glecaprevir/Pibrentasvir and five with Sofosbuvir/Velpatasvir.

To date 6 patients have completed antiviral (DAA) treatment. All patients have become undetectable on treatment. Treatment choice has been principally influenced by renal function at the time of initiation. None of the patients had a clinically significant increase in aminotransferase levels.

All patients in Cardiff are treated with tacrolimus and mycophenolate mofetil (with or without steroids) as maintenance immunosuppression with regular monitoring of tacrolimus levels. Post transplantation kidney function has been good; mean eGFR 51 ml/min (IQR 38 ml/min–65 ml/min). One patient underwent graft nephrectomy 10 days post transplant due to renal vein thrombosis (not related to HCV or DAA therapy). SVR 12 data will be presented at the conference.

Conclusion: The first cases of transplant of HCV positive donors to HCV negative recipients in the UK are presented. The success of these first cases warrants consideration for wider adoption of this practice in line with UK Position Statement on the use of organs from Hepatitis C viraemic Donors and increased infectious risk donors in Hepatitis C negative recipients.

THU342

Pharmacy-based molecular point-of-care testing for hepatitis C (HCV) in high-risk patients: feasibility and linkage to care

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Background and Aims: Achieving HCV elimination will require novel approaches to testing and treatment, particularly in high-risk patient groups, such as people who inject drugs, who may not readily access or engage with healthcare. Testing methods that are both easy to deliver and are acceptable to patients are essential. This study aimed to assess the feasibility of delivering rapid molecular HCV testing using the Cepheid® GeneXpert IV:II within community pharmacies and subsequent linkage to care.

Method: Eight community pharmacies within Leicestershire, England, were invited to take part. All had established needle exchange and/or opiate substitution therapy programmes and had facility for a private consultation room. Individual pharmacists received training on use of the GeneXpert platform, as well as the consent and testing process. Patients returned after 1-hour to receive their result or at an agreed alternative time.

Results: Over a nine-week period a total of 203 tests were performed at 6/8 pharmacies, with the majority (92%) undertaken by three pharmacies. 30 (15%) patients were found to have detectable HCV RNA, with a median HCV RNA of 715500 IU/ml. Of these, 20 (66%) were not previously known to the Leicester treatment network. All positive patients were offered a clinic appointment and to date 20 (66%) have attended. 12 (40%) of the 30 positive patients have now completed treatment and one is due to commence imminently. 2 patients (7%) were ineligible for treatment on clinical grounds (pregnancy and spontaneous clearance), 2 (7%) defaulted from further follow-up, 2 (7%) are under ongoing review and one patient declined treatment.

Conclusion: Our study has shown that hepatitis C testing of high-risk patients using Cepheid® GeneXpert within a pharmacy setting was feasible and that subsequent linkage to care was achieved in two thirds of all positive cases. Rapid HCV RNA results offers a same-day result, which may be advantageous over antibody testing methods such dried blood spot, and implementation on a wider scale could play an important role in achieving HCV eradication.

THU343

Improving female street sex worker (FSSW) access to hepatitis C testing and treatment

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Background and Aims: Female Street Sex Workers (FSSWs) have high rates of substance misuse and sexually transmitted infections, which are a key contributors to the increased incidence of HCV infection seen in this population. If the WHO target to eliminate HCV is to be met, this group will require specific test and treat strategies. Two local charities (The Joanna Project and Basis Yorkshire) who work closely with FSSWs were identified to work with during the project. A previous survey had identified that venepuncture and travelling to healthcare facilities were significant barriers to accessing testing and treatment for HCV. The aim of the study was to improve access to treatment for FSSWs without the need for direct engagement with health services.

Method: Over a 12 weeks period in 2018 FSSWs working in Leeds were approached in support facilities/charity premises and offered counselling and dry blood spot HCV antibody testing with subsequent capillary blood PCR testing in the local laboratory. Any patient testing PCR positive was offered pan genotypic HCV treatment with

Epclusa® or Maviret® within the charity premises after checking for drug drug interactions with their prescribed and non-prescribed medication.

Results: 46 FSSWs were tested during the 12 week period. 22/46 (47.8%) of those FSSWs tested were HCV antibody positive and 18/46 (39.1%) were HCV PCR positive indicating very high prevalence rates in line with their known high risk behaviour. Of those 18 PCR positive patients 13 commenced HCV treatment, three patients declined treatment and two are continuing to consider whether to be treated or not.

Outcomes - RNA Positive	No of FSSW	Outcomes - RNA Positive	No of FSSW
Started Treatment	13	Declined Assessment	0
Declined Treatment	3	Considering Treatment	2

Figure: Treatment Commencement for FSSW testing HCV PCR positive.

Conclusion: FSSWs have a very high prevalence of HCV PCR positivity but are willing to be treated for HCV if this service is provided outside of a healthcare centre and does not involve venepuncture. Following up this group post treatment to ensure cure and reduce risks of reinfection is also likely to be a challenging despite ongoing support and education in the charity sector.

THU344

Screening and treatment difficulties of hepatitis C virus infected patients with substance use disorders or dual pathology, despite centralized management in an addiction and dual diagnosis center

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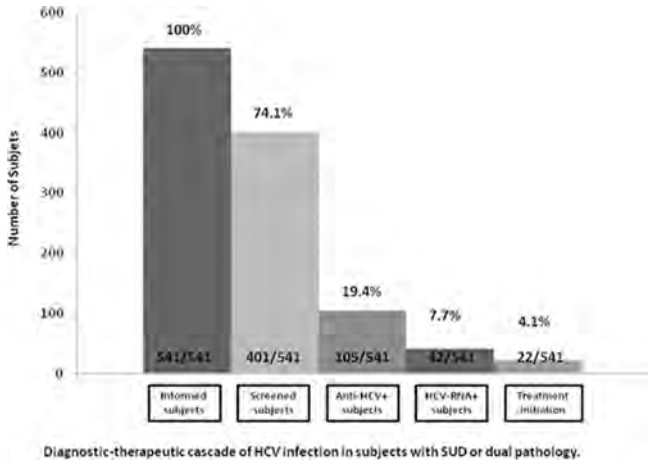
Background and Aims: WHO goal is to eliminate hepatitis C virus (HCV) infection as a public health threat by 2030. In order to achieve this target, screening and treatment strategies for risk populations with poor access to the health system are necessary. The objective of the study was to establish an HCV screening and treatment program for subjects with substance use disorders (SUD) or dual pathology (psychiatric plus SUD) treated in an Addiction and Dual Diagnosis Center (ADDC).

Method: Prospective study for screening and treatment of HCV in subjects with SUD or dual pathology followed in an ADDC from November 2018 to June 2019. Anti-HCV antibodies were determined with reflected HCV-RNA determination. In those HCV-RNA positive cases the liver lesion was evaluated and the treatment started at the ADDC.

Results: The study was proposed to 541 subjects and 401 (74%) accepted. 75% were male, the average age was 45 years and 61% had dual pathology. 105 (26.2%) were anti-HCV positive and 42 (10.5%) HCV-RNA positive. Treatment was only initiated to 22 subjects due to the high loss of follow-up. Those anti-HCV positive had higher frequency of poly-drug abuse ($p < 0.001$), need for internalization in therapeutic communities ($p < 0.001$), SUD to illegal substances ($p < 0.001$), use of injected drugs ($p < 0.001$), number of overdose episodes ($p < 0.001$), use of opioid substitution therapy ($p < 0.001$), personality disorders ($p = 0.02$) and psychotic symptoms due to substance abuse ($p < 0.001$).

Those HCV-RNA positive subjects were in larger proportion women ($p = 0.02$), younger ($p = 0.003$), with more cocaine consumption in the last 6 months ($p = 0.02$) and greater deterioration in mental quality of life ($p = 0.04$) than HCV-RNA negative.



Diagnostic-therapeutic cascade of HCV infection in subjects with SUD or dual pathology.

Conclusion: There is a significant difficulty in the screening and treatment of HCV in subjects with SUD or dual pathology probably related to their underlying pathology. The HCV-RNA positive are often young women with greater cocaine consumption and more deterioration of the mental quality of life.

THU345

Integrating hepatitis C virus screening by dry blood spot test into colorectal cancer screening: a randomized controlled trial

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Background and Aims: To achieve WHO goals for the elimination of hepatitis C virus (HCV) infection by 2030 screening is mandatory, and targeting high prevalence groups such as birth cohorts adults is a good option. Currently, in our health care setting this population is being invited for colorectal cancer (CRC) screening with biennial fecal immunochemical testing (FIT). Integrating a simplified diagnostic tool such as the dry blood spot test (DBS) to FIT screening could be of great help for HCV microelimination. However, it is unknown if both screening strategies interfere regarding participation. This study was aimed to study whether adding DBS to FIT CRC screening may improve HCV screening adherence.

Method: A randomized controlled trial (NCT04037046) was conducted in asymptomatic individuals aged 50–70 years, attended by four general practitioners (GPs) in our area. Participants (n = 609) were stratified by age, sex and address and randomized to one of three groups: 1) HCV (DBS kit) screening at the healthcare center, following invitation letter and appointment with their GP; 2) Combined screening for HCV and CRC (FIT kit); and 3) Self-testing screening for HVC and CRC with pre-sealed envelope for sending kit samples to the central laboratory. DBS were positive if >15UI (Cobas 6800®) and FIT ≥ 20ug/g feces (OC-Sensor kit®).

Results: Among randomized patients (mean 59.4 ± 5.4 years, 51.2% male), and excluding 7.3% after not receiving postal mail, 132 (23.3%) subjects participated with test delivery in a median of 30.5 days (IQR 13.8–46.2); 30% in DBS, 28.4% in DBS+FIT and 13.5% in the self-testing strategy ($p < 0.01$). In the first two strategies, 38.7% and 25.2% had previous opportunistic screening with FIT or colonoscopy respectively, and 9% had performed a serology for HCV. No differences

between groups were observed. Patients in the DBS strategy compared to DBS+FIT were higher alcohol consumers (p = 0.028). All DBS and FIT sent to the center for analysis were considered valid (including self-testing samples), with 0.81% of viremia and 12.3% of positives, respectively.
Conclusion: HCV screening by invitation letter from GPs to perform DBS in the healthcare center is equally accepted when it is associated with CRC screening by FIT, and independently of the previous testing for CRC or HCV. This integrating screening strategy can be particularly useful in healthcare areas where CCR screening program are widely implemented with a high participation rate.

THU346
Ethnic disparities in the risk of hepatitis C virus-related diabetes in a large population-based cohort in Canada
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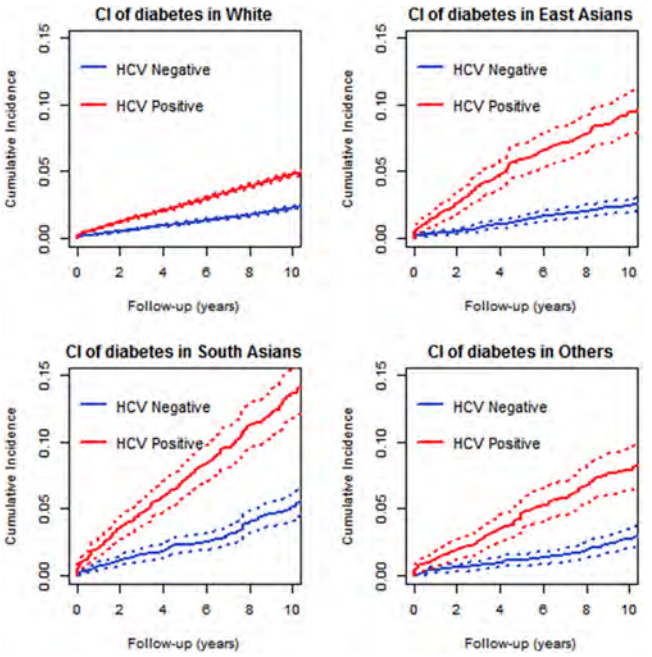
Background and Aims: There is increasing evidence that persons living with hepatitis C virus (HCV) infection are at a higher risk of type 2 diabetes (T2D). Studies based in multi-ethnic settings have shown an ethnic disparity in diabetes, with an increased risk in non-White populations. Thus, the impact of HCV infection on diabetes incidence may differ across ethnic groups. This study assessed the impact of HCV on diabetes incidence within a large ethnically diverse population-based cohort. We conducted stratified analyses to examine the ethnic disparity.
Method: The incidence of T2D by HCV status was assessed in the British Columbia (BC) Hepatitis Testers Cohort, which includes ~1.7 million individuals tested or reported as a case of HCV in BC, linked with various health administrative data. Diabetes was defined using a validated algorithm modified with data on prescription drug dispensation. Individuals tested for HCV since 1990 were followed from the date of their first positive or last negative HCV RNA test to the earliest of 1) incident type 2 diabetes, 2) death or 3) end of study (12/31/2015). Propensity scores (PS) were estimated based on age at HCV diagnosis, duration of follow up and other key covariates and HCV-positive and negative individuals were matched at a 1:1 ratio without replacement. We used Fine and Gray competing risk models adjusted with potential confounders to estimate hazard ratios and 95% confidence intervals for incident diabetes, overall, and stratified by ethnicity.
Results: After PS matching, the study sample included 117,192 individuals. When adjusted for potential confounders and competing risk of mortality, HCV infection was significantly associated with incident T2D, with an adjusted hazard ratio of 2.32 (95% CI 2.20–2.46). Other characteristics significantly associated with an increased risk of T2D included older age at diagnosis, non-White ethnicities, material deprivation, obesity, having a mood and anxiety disorder, problematic alcohol use and injection drug use. When stratified by ethnicity, cumulative incidence of T2D was higher for HCV positive individuals in non-White populations (figure).



Conclusion: This analysis supports other studies that HCV infection is associated with a higher risk of developing diabetes. Furthermore, this risk was amplified among non-White populations. The findings of this study highlight the need for continued care and screening for HCV-related chronic diseases such as diabetes in individuals living with HCV infection especially among Asian populations.

THU347
The electronegative low-density lipoprotein in patients with chronic hepatitis C infection
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Background and Aims: Patients with chronic hepatitis C virus (HCV) infections have shown to have significantly higher mortality such as increased incidence of cancer and cancer-related mortality and extrahepatic diseases such as cardiovascular diseases and cerebral vascular diseases (CVD) than the general population. Nevertheless, patients with HCV infection display significantly decreased triglyceride, total cholesterol, high density lipoprotein-cholesterol (LDL-C) and low density lipoprotein-cholesterol (LDL-C) level in plasma. Plasma LDL has been classified into five charge-defined sub-fractions LDL L1, L2, L3, L4 and L5 using anion-exchange chromatography and L5, the most negatively charged LDL, is more abundant in patients with increased cardiac risks than in the healthy population. The present study aimed to investigate the relationship between the HCV infection and serum LDL L5 level and the impact of the antiviral therapy on the serum LDL L5 level.
Method: Patients with CHC and controls were enrolled in the present study. Patients treated with direct antiviral agents (DAAs) were enrolled for testing the serial change of the L5 at baseline, end-of-treatment (EOT) and end-of-follow up (EOF) which is the 12 weeks after cessation of therapy with definition of the sustained virological response (SVR12). Laboratory data were collected and plasma were tested for the LDL 5 sub-fractions (L1, L2, L3, L4, and L5) using the increasing negative charge on anion-exchange columns. L5% means

percent of L5 in total LDL. L5 concentration ([L5]) estimated by L5%* LDL-C.
Results: Total 477 subjects enrolled into the study. There were 167 (35.0%) with negative anti-HCV and 310 (65.0%) with positive anti-HCV and 73 subjects with the baseline, EOT and EOF samples after DAA treatment for testing the L5% and [L5]. The L5% was an independent risk factor associated with for HCV infection (the risk of L5% >1.8 was approximately ten-fold (OR = 10.28) and the risk of L5% >5 (OR = 8.1) was approximately eight-fold after adjusting the other risk factors. The anti-HCV positivity was the only factor significantly associated with the risk of L5%>1.8 in multivariate analyses. Among patients with HCV infection, L5% was significantly associated with ALT and platelet levels. For patients with DAA therapy, plasma L5 (%) and [L5] significantly decreased by successful anti-viral treatment ($p < 0.0001$ for L5% and $p = 0.0018$ for [L5]).
Conclusion: LDL L5, showing an increased level compared to controls, indicates that it can be used as a new biomaker for liver-related disease caused by HCV infection. Although the elevated serum lipid profile has been noted after successful DAA therapy, the decreased level of L5 after cure of the HCV RNA implicate a role in the decreased risk of CVD.

THU348
Telemedicine and decentralized treatment dispensation to rescue patients in a hepatitis C micro-elimination program based on on-site dried blood spot testing in drug addiction centers

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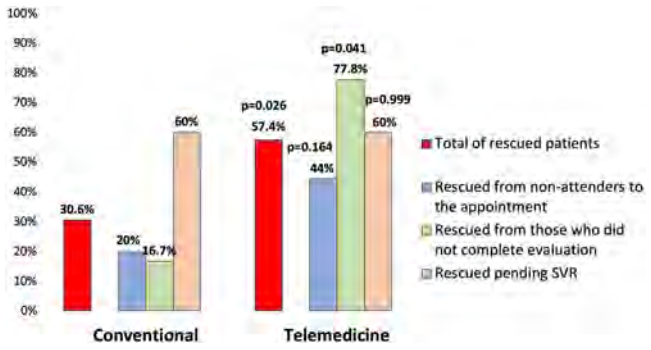
Background and Aims: Despite incorporating decentralized tests such as on-site dried blood spot testing (DBS) in Drug Addiction Centers (DAC) to facilitate HCV care cascade, a high percentage of patients drop-out, mainly due to socioeconomic reasons. This fact is a further barrier to reach WHO elimination goals by 2030. Our aim was to evaluate if telemedicine linked to a decentralized dispensation of HCV treatment is a feasible and effective strategy to rescue dropouts in this model of care.
Method: Between January 2017 to July 2018, patients lost to follow-up from a micro-elimination plan in DAC based on anti-HCV DBS testing were registered. These patients were proposed to RNA DBS testing (Cobas 6800©) and according to the center: a) telemedicine (Webex-Cisco©), and DAC staff-led model of treatment dispensation, or b) schedule an appointment with the specialist as the conventional model. A questionnarie for the assessment of patient satisfaction with realtime telemedicine was performed to participants.
Results: Among 512 prospective participants, 178 patients were positive for anti-HCV and were scheduled with the specialist. 55.6% (n = 99 of these patients did not complete the program (85.5% male, 46 ± 9.5 years): 44 patients were non-attenders to the appointment with the specialist, 25 patients did not complete the evaluation and 30 patients (among 68 treated) were pending assessment for sustained virological response. The number of rescued patients that completed the program was significantly higher in the telemedicine group than in the conventional model (57.4% vs. 30.6%, $p = 0.026$), especially in those patients with a previous incomplete evaluation (77.8% vs. 16.7%, $p = 0.041$) (see figure). Patients satisfaction with telemedicine care was excellent among participants.



Conclusion: Telemedicine linked to a decentralized model for HCV treatment dispensation, as an interventional strategy in a program based on on-site diagnosis, is well accepted and effective to rescue patients previously lost to follow-up in DAC, facilitating micro-elimination in this priority population.

THU349
The success of outreach hepatitis C screening among a Belgian population of drug users in a rural and urban setting

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Background and Aims: Hepatitis C viral (HCV) infection is most prevalent in people who use drugs (PWUD). In Belgium, all PWUD have access to needle-syringe programs (NSP) and low threshold opioid agonist therapy (OAT). Various local initiatives to screen for HCV in addiction care centers providing OAT have already been successful. However, groups such as ex-PWUD or people who inject stimulants are mostly unreached. There are also no good estimates of the size and characteristics of these subgroups in Belgium. We want to outreach to PWUD who are not connected to OAT centers, using screening for HCV as a bridge to re-integration in medical care.
Method: This study was carried out simultaneously in Antwerp (urban) and Limburg (rural), Belgium. The participants were recruited by outreaching at organised screening events on different locations. The location of these events were communicated in advance, using posters and flyers and planned in accordance with local authorities, health care workers and peers. The eligible candidates (>18 years and PWUD) were tested by finger prick for HCV antibodies (Ab) using OraQuick®. While waiting for the results, an encoded questionnaire was filled out. An incentive of €10 was provided to participants after receiving their results.
Results: A total of 425 PWUD were reached and tested for HCV Ab. Out of all PWUD 148 (34.8%) had ever injected drugs (PWID). In relation to intravenous (IV) use of stimulants, people in an urban setting were more likely to inject amphetamines though there was no difference in IV use of cocaine (Table 1). Although every PWID in Belgium has access to NSP and low-threshold OAT still not everyone was connected (Table 1). HCV Ab was present in 14.8% and was more prevalent in the urban setting (Table 1).

	Antwerp (n=207)	Limburg (n=218)	p-value
PWID	68 (32.9%)	80 (36.7%)	0.233
IV amphetamine	47/68 (69.1%)	40/80 (50.0%)	**0.014**
IV cocaine	49/68 (72.1%)	47/80 (58.8%)	0.064
Recently (<6m) injected **not** connected to NSP (n=73)	5/42 (11.9%)	8/31(25.8%)	0.095
Recently (<6m) used opioid **not** connected to OAT (n=97)	27/54 (50.0%)	22/43 (51.2%)	0.536
HCV Ab +	38 (18.4%)	25 (11.5%)	**0.031**

Figure: (abstract: THU349)

Conclusion: The outreach method worked to contact and screen a group of PWUD not connected to care. Of these, more than half were (former) amphetamine injectors. An important part of the study group was positive for HCV Ab and the prevalence was higher in an urban setting. Although Belgium is a country with low-threshold access to addiction care not everyone was connected neither in an urban or rural setting.

THU350

Angiopoietin 2 levels decrease with SVR and correlate with dynamics of portal hypertension in patients with HCV-induced advanced chronic liver disease

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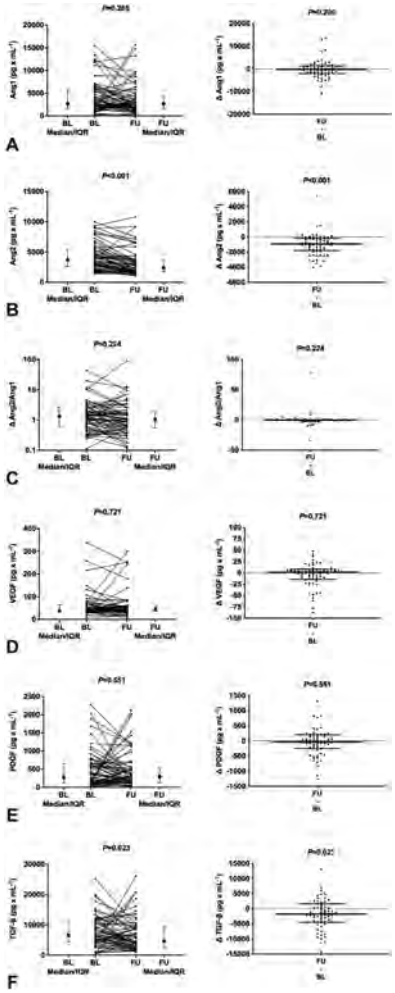
Background and Aims: Sustained virologic response (SVR) decrease hepatic venous pressure gradient (HVPG) in patients with HCV-induced advanced chronic liver disease (ACLD), which translates into a clinically meaningful benefit. We recently identified a panel of cytokines reflecting hepatic angiogenesis, fibrogenesis, and hepatocarcinogenesis that were increased in patients with persistent necroinflammatory activity despite HCV cure, which in turn resulted in lower rates of hemodynamic response. In the present study, we aimed to investigate (I) the impact of HCV cure on plasma levels of biomarkers of hepatic angiogenesis (angiopoietin 1 [Ang1], 2 [Ang2], and vascular endothelial growth factor [VEGF]) as well as fibrogenesis and hepatocarcinogenesis (platelet derived growth factor [PDGF] and transforming growth factor β [TGF-β]). Moreover, we assessed (II) the relationship between changes in these cytokines and HVPG.
Method: Pre- (baseline [BL]) and post-treatment follow-up [FU] plasma levels of cytokines and von Willebrand factor (VWF) as well as HVPG were assessed in 66 patients with ACLD and pre-treatment portal hypertension (HVPG ≥6 mmHg) who achieved SVR to interferon (IFN)-free therapy.
Results: At BL, the majority of patients were Child-Turcotte-Pugh (CTP) A, while 26% percent of patients were CTP B. Median MELD was 9 (interquartile range [IQR]: 3) points, median HVPG was 12.5 (IQR: 8) mmHg, and 68% of patients had clinically significant portal hypertension (CSPH; HVPG ≥ 10mmHg).
HCV cure induced profound decreases in Ang2 (Figure; panel B) and also decreased plasma levels of TGF-β (F), while Ang1 (A), the ratio between Ang2/Ang1 (C), VEGF (D), and PDGF (E) remained unaffected. Patients with CSPH at BL achieving an HVPG-decrease ≥ 10% had a more pronounced relative decreases in Ang2 (−34.5 [IQR: 30.3]%), as compared to patients without an HVPG-response (−13.5 [IQR: 31.2]%); P = 0.041). Moreover, relative changes in Ang2 showed direct correlations with relative changes in HVPG (Spearman's ρ = 0.276; P = 0.029), as well as with relative changes in VWF levels (Spearman's ρ = 0.324; P = 0.009).



Conclusion: Plasma levels of Ang2 - which have been previously linked to liver fibrosis and de-novo hepatocellular carcinoma after antiviral therapy - substantially decreased after SVR. Interestingly, decreases in Ang2 were more pronounced in patients achieving an HVPG-decrease ≥ 10%. Moreover, changes in Ang2 correlated with the dynamics of portal hypertension as well as VWF, a marker of endothelial dysfunction that confers additional HVPG-independent prognostic information. Finally, HCV-cure also decreased plasma levels of the key profibrotic and oncogenic cytokine TGF-β.

THU351

A program of hepatitis C surveillance with linkage to care for inpatients from non-infectious departments in two tertiary hospitals from Jiangsu, China

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Background and Aims: An estimated 20 million Chinese are chronically infected with hepatitis C virus (HCV). However, the majority are unware of their HCV diagnosis and few are treated. A retrospective study from our tertiary hospital in China indicated a lack of knowledge of non-infectious departments (non-ID) physicians regarding the criteria of HCV antibody screening and an insufficient follow-up of patients with positive HCV antibody (Ab) from non-IDs. Therefore, we designed and evaluated a compressive hospital-led program for enhanced HCV surveillance with linkage to care in non-IDs of hospitals, with the goal to expand HCV surveillance and enhance follow-up of potential HCV patients with access to treatment at hospital level.
Method: This program was launched in two tertiary hospitals in Jiangsu province of China. The program consisted of an educational campaign to raise awareness of physicians from non-IDs to expand HCV surveillance; a new HCV clinical algorithm responsible for efficient follow-up of patients with positive HCV Ab; and comprehensive testing, diagnosis, and treatment. In our new HCV clinical algorithm, firstly HCV Ab testing is expanded among the inpatients who meet the criteria of HCV surveillance. Further, for those patients with positive Ab, the physician-in-charge invited ID physicians for the joint consultation regarding RNA PCR testing and the possible referral in near future. Once HCV infection is diagnosed, the ID nurse follow up with the patients and schedule appointments of HCV clinics.
Results: With our new launched program of hepatitis C Surveillance with linkage to care for the last 8 months (from Mar 2019 to Oct 2019), a total of 68.7% (64,111/93,291) of inpatients had HCV Ab screen test. Among them, 0.54% (343/64,111) of non-ID inpatients were found with positive HCV Ab. While 81.9% patients were enrolled in our study, 100% (281/281) of patients with positive HCV Ab was followed up for HCV RNA PCR testing, and 42.5% (119/281) of patients were HCV RNA positive. Currently, 71.4% (85/119) of HCV patients were linked to care, 57.6% (49/85) started DAA treatment.
Conclusion: This hospital-led educate, test and treat demonstration project achieved enhanced HCV Surveillance with linkage to care. This approach could be an important strategy in hospital setting to improve the hepatitis C care continuum by identifying individuals unaware of their HCV status and facilitating their access to HCV treatment.

THU352

Feasibility and acceptability of self-testing for hepatitis C infection among the general population in Egypt

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Background and Aims: Insufficient testing coverage is a major barrier to hepatitis C virus (HCV) elimination. Self-testing, a process in which people can collect their own specimen, perform a test and interpret the result, often in private or with someone they trust, has been very successful in promoting uptake of HIV testing. As for HIV, it is considered that introduction self-testing for HCV infection has a high potential to expand the coverage of HCV testing services. In order to evaluate feasibility and acceptability of HCV self-testing in HCV-prevalent settings, FIND has conducted a pilot observational study in Mansoura region, Egypt.
Method: Prospective cross-sectional study conducted in two hospitals located in Mansoura region. Prototype OraQuick® HCV Self-Test developed by OraSure Technologies (US) was used to perform self-testing from oral fluids. Hospital staff screened and recruited eligible participants, sought informed consent and demonstrated the use of the OraQuick® HCV Self-Test. The participant then used the OraQuick® HCV Self-Test while observed by a study staff who documented errors made and difficulties faced during the testing procedure. Upon the completion of the testing, all participants were administered a multiple-choice questionnaire asking about acceptability and usability of the self-test. All participants were tested by a hospital staff on professional use OraQuick® HCV Rapid Diagnostic Test and results of professional use test and self-testing were compared.
Results: A total of 116 participants were recruited in the study, out of which 17 (15%) could not read. The majority (87%) of participants completed self-testing without any assistance. More than 95% completed each step of the testing correctly and found the procedure to be easy (52%) or very easy (44%). Almost all participants (99%) indicated that they would recommend HCV self-test to friends and family and over 96% would use the self-test again if it was available. Majority (97%) also said that they would contact a healthcare facility if results of self-testing were positive, and 67% knew that HCV can be cured. While 65% of the participants preferred oral fluid-based test, 24% indicated that they would rather use blood-based test for self-testing. Concordance between the results of self-testing and professional use OraQuick® HCV Rapid Diagnostic Test was 89% (Kappa 0.66).
Conclusion: This study demonstrates high acceptability and usability of oral fluid-based self-testing for HCV. This additional approach has a potential to increase uptake of HCV testing services in settings with high awareness of HCV infection. Further research of acceptability and feasibility in high-risk populations as well as evaluation of performance of HCV self-tests is underway.

THU353

The HSD17B13 rs6834314 variant is associated with liver stiffness measurement in untreated HCV-3 patients with cirrhosis

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Background and Aims: Recently, the single-nucleotide polymorphism (SNP) rs6834314 near to the 17-beta hydroxysteroid dehydrogenase 13 (HSD17B13) gene has been associated with NAFLD histology. Particularly, the minor G allele of the rs6834314 variant correlated with increased steatosis but decreased inflammation. This study aimed to analyzed the correlation between the rs6834314 genotypes and liver stiffness measurement (LSM) in chronic hepatitis C (CHC) patients.
Method: 410 Caucasian CHC cirrhotic patients were retrospectively enrolled in a single Hepatology centre: median age 64 (28–87) years, 57% males, BMI 25 (16–40) Kg/m^2, ALT 75 (10–770) U/L, LSM 17.5 (12–75) kPa, and 19% with diabetes. HSD17B13 rs6834314 was genotyped by TaqMan allelic discrimination assay (Applied Biosystems).
Results: HSD17B13 rs6834314 genotype was AA in 251 (61%), AG in 143 (35%) and GG in 16 (4%). Overall, the rs6834314 variant showed no association with median baseline LSM values: 17.8 (95%CI 17,2–19,1) kPa in AA vs 17.0 (95%CI 15,4–18,3) kPa in AG/GG, ($p = 0.24$). Stratifying patients according to hepatitis C virus (HCV)-genotypes, we found that in HCV-3 patients ($n = 41$) median LSM values significantly differed according to rs684314 genotypes: 25.8 (95%CI 18.5–28.3) kPa in AA vs 15.4 (95%CI 13.1–20.3) kPa in AG/GG ($p = 0.014$), unlike to HCV-1: 18.2 (95%CI 16,9–21) kPa in AA vs 17.3 (95% CI 15,0–19,6) kPa in AG/GG ($p = 0.13$), HCV-2: 18.5 (95%CI 17,1–22,3) kPa in AA vs 16.9 (95%CI 13,1–20,9) kPa in AG/GG ($p = 0.30$), and HCV-4: 19.8 (95%CI 17,3–21,6) kPa in AA vs 21.2 (95%CI 17,1–31,0) kPa in AG/GG ($p = 0.22$). Moreover, in the HCV-3 subgroup the prevalence of patients with increased risk of significant portal hypertension (i.e. those with LSM ≥ 25 kPa) was higher in AA than in AG/GG carriers (56% vs. 17%, $p = 0.01$). Multivariate binary logistic regression analysis

confirmed that in HCV-3 cirrhotics, the minor G allele of rs6834314 reduces the risk of exceed the LSM 25 kPa cut-off more than nine fold (OR 0.11, 95%CI 0.02–0.62, p = 0.013) together with age (OR 0.9, 95%CI 0.76–0.99, p = 0.03) and independently of gender, BMI, ALT, diabetes and PNPLA3 rs738409 polymorphism.
Conclusion: In untreated HCV-3 cirrhotics, the rs6834314 variant was associated with lower LSM values suggesting that the correlation between HSD17B13 SNP and liver disease severity might be triggered mainly by virus-mediated steatosis.

THU354
The impact of universal access to DAA and real-world treatment outcome amongst genotype 3 hepatitis C virus-infected prisoners
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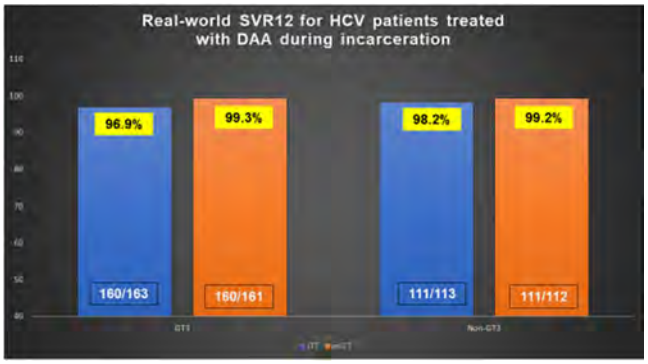
Background: Despite the disproportionally high prevalence of hepatitis C virus (HCV) amongst prisoners, eradication remains challenging due to logistic and financial barriers. Genotype-3 (GT3) was considered difficult to treat even with the introduction of direct-acting antiviral (DAA). To date, the real-world treatment outcomes of GT3 HCV prisoners with DAA remains limited.
Objective: To compare the real-world efficacy of DAA and the impact of universal access of DAA among GT3 and non-GT3 HCV prisoners.
Method: 307 HCV prisoners treated with DAA in our specialized liver clinic from 2013–2019 were prospectively included in a treatment database and sustained virological responses at 12 weeks (SVR12) were compared. Universal access to pan-genotypic DAA was commenced in 2019. GT3 HCV patients received either 12 weeks of sofosbuvir/daclatasvir and ribavirin (SOF/DAC/Riba) or 12-weeks of sofosbuvir/velpastavir (SOF/VEL). Genotype 1 (GT1) patients receive HARVONI, VIEKIRA PAK or SOF/VEL for 12 weeks. Ribavirin was added for patients with clinically significant portal hypertension, prior treatment or hepatocellular carcinoma.



Results: GT3 (57.7%) was the commonest genotype followed by GT1 (39.7%) amongst prisoners. Patients were mostly male (93.2%) and cirrhotic (52.1%), with a mean age of 52.5 years. The majority received SOF/VEL +/– ribavirin (58.9%) followed by VIEKIRA PAK +/– ribavirin (23.2%) and SOF/DAC/Riba (14.7%). The overall SVR12 based on intention-to-treat (ITT) and modified ITT analysis for GT3 and GT1 were 96.9%, 99.3% and 98.2%, 99.2%, respectively (Figure 1). While virological failure occurred in SOF/DAC/Riba (n = 1) and VIEKIRA PAK (n = 1), there was no virological failure using SOF/VEL regimen. The SVR12 was similar between GT3 and non-GT3 prisoners after adjusted to platelet count, PT and baseline viral load (99.4% vs 99.2%,95%CI: 0.03–76.7). Compared to the year 2018, universal access to pan-genotypic DAA alone significantly improved treatment access among HCV prisoners by 130% and allowed more non-cirrhotic HCV prisoners to be treated in 2019 (62.1% vs 42.6%, p < 0.001).
Conclusion: We demonstrated that GT3 HCV prisoner is no longer a difficult-to-treat cohort in the pan-genotypic DAA era, and high SVR12 can be achieved in the real-world setting. Our result shows that universal access to DAA among HCV prisoners is an impactful strategy for HCV micro-elimination in this cohort.

THU355
Hepatitis C reflex testing in Spain in 2019: a story of success
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Background and Aims: For exploring the diagnosis situation of hepatitis C virus (HCV) infection in Spain, in 2017 we conducted a survey across hospital diagnostic laboratories, finding that only 31% of them were providing reflex testing (HCV antibodies and HCV RNA on the same sample). As a consequence, the Spanish Societies of Infectious Disease & Clinical Microbiology (GEHEP-SEIMC), Hepatology (AEEH, SEPD) and the Viral Hepatitis Elimination Alliance (AEHVE) signed a position document with recommendations on reflex testing. In addition, training and dissemination activities were developed by the mentioned organizations to promote reflex testing implementation in the Spanish hospitals. Our aim was to evaluate how reflex testing has been implemented in Spain, and to gain knowledge on access to new diagnostic strategies across hospital Spanish laboratories.
Method: Cross-sectional study with data collection through a survey addressed to hospitals of the Hospitals National Catalogue with the following inclusion criteria: 1) general hospital (monographic, e.g., psychiatric hospitals are excluded); 2) with at least 200 beds; and 3) public, or teaching hospital if private. A questionnaire with the variables of interest, designed by a scientific committee composed of hepatologists and microbiologists, was sent to the selected hospitals. The fieldwork was carried out in September and October 2019.
Results: In 2019, 161 hospitals were surveyed, and 129 (80,1%) responded, vs 90/160 (56,3%) who responded in 2017 (p < 0,001). Reflex testing is now implemented in 89% of Spanish hospitals (115/129); in 2017 only 31% (28/90; p < 0,001) performed reflex testing. The number of hospitals that implemented alert systems to communicate HCV active chronic infection rose from 68,9% (2017) to 86,0% (2019) (p = 0,002). Access to dried blood spot (DBS) and/or point of care testing in 2019 in Spain was: 10,9% for antibody testing from DBS; 15,5% for RNA testing from DBS; 36,4% for point of care (POC) RNA testing; 0,85% for antibody POC testing. Overall, 43,4% of Spanish hospitals has access to at least one of DBS/POC testing strategies.
Conclusion: In Spain, the proportion of hospitals that perform reflex testing for chronic HCV infection has significantly increased to 89% in 2019. Recommendations, training and dissemination measures performed since 2017 may be responsible for this increase. However, in 2019 new screening strategies such as DBS and POC testing are poorly implemented in Spanish hospitals.

THU356

Cracks in the hepatitis C cascade of care: real-life outreach data from four Central London services

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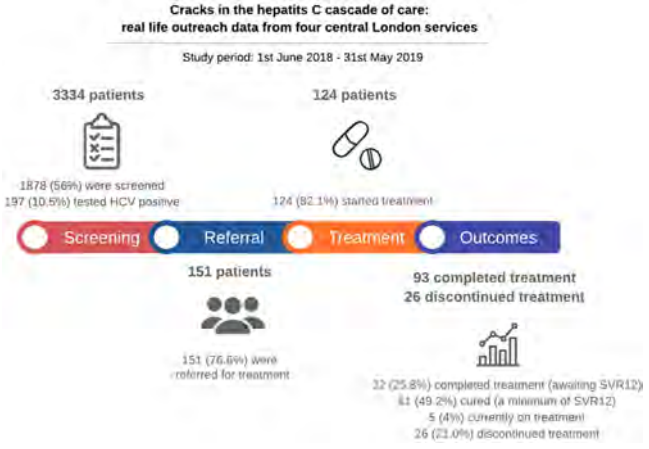
Background and Aims: The standard Hepatitis C (HCV) care pathway incorporates multiple appointments for screening, referral, treatment and post-treatment follow up. However, at-risk patient populations often have multiple factors complicating treatment engagement, such as concurrent mental health diagnoses, no fixed abode, substance misuse and incarceration. Hence patients fall through cracks even before reaching the treatment stage. We reviewed data from four outreach clinics which target the at-risk patient population and aim to identify the main gaps where patients are lost in the cascade of care.

Method: We retrospectively analysed data from four outreach clinics in central London, collecting data from electronic patient records systems for patients attending from 1st June 2018 to 31st May 2019. Variables measured included numbers tested for HCV, referred for direct-acting antiviral (DAA) therapy, started on treatment and treatment outcomes.

Results: 3334 patients presented to these four outreach clinics over the one year period. 1878 (56%) patients were screened for HCV. 339 (18.1%) patients tested positive for anti-HCV and 197 (10.5%) were HCV viraemic. Of these 197, 151 (76.6%) were referred for treatment and 124 (62.9%) were started on therapy. At the end of the one-year period, 93 (75%) patients had completed treatment and achieved SVR12 (61, 49.2%) or were awaiting SVR12 (32, 25.8%). 5 (4%) were on continuing treatment. 26 (21%) patients discontinued treatment. Testing methods and time of testing differed between the four services, which offered venepuncture and opt-out testing (91.6% uptake), dried blood spots at triage (71.1% uptake), and venepuncture if clinically indicated (44.1% and 28.3%).



Conclusion: Opt-out testing at registration delivered the highest uptake (91.6%). Lower uptakes were seen at services where venepuncture testing was offered depending on clinical assessment. 10.5% of tested patients in this high-risk cohort were HCV viraemic. However, 44% were not tested and 23.4% of viraemic patients were not referred for treatment as they lacked baseline diagnostics. A further 13.7% did not attend to start treatment. Of those who began treatment, >75% were cured or await cure confirmation. Therefore, to improve outcomes and reduce cracks in the cascade for this marginalised population, a same-day testing and treatment approach would potentially improve overall care.

THU357

Seroprevalence of hepatitis B virus co-infection among HCV infected patients screened during the national campaign for HCV eradication in Egypt

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Background and Aims: Viral hepatitis is a major health problem in Egypt meanwhile, little is known about the true prevalence of hepatitis B virus (HBV) co-infection in Hepatitis C virus (HCV) patients and its risk factors. This multicenter nationwide study aimed to assess the seroprevalence of HBV among Egyptian patients with HCV and its possible risk factors.

Method: This is a cross section, multicentre, nationwide study. Data was extracted from database of the National Network of Treatment Centres (NNTC) affiliated to National Committee for Control of Viral Hepatitis (NCCVH), Ministry of Health, Egypt. Baseline data of patients screened and proved to be infected with HCV (by positive antibody) and viremic (by HCV RNA PCR) during the national campaign for HCV eradication (October 2018-April 2019) was retrieved. The data collected included: demographic data, laboratory investigations including (HBsAg, complete blood count, liver biochemical profile, serum creatinine, AFP, HBA1c, viral load), FIB-4 calculation and abdominal ultrasound results. Statistical analysis was done.

Table 1: Demographics and laboratory results of HBV/HCV co-infection versus HCV mono-infection

	HBsAg positive (n = 2,347)	HBsAg negative (n = 295,618)	P value
Age (years)	51.08 ± 13	51.57 ± 14	0.08
BMI (kg/m^2)	29.2 ± 7.6	29.6 ± 7.2	0.95
ALT (U/L)	47.48 ± 29.7	47.43 ± 45.5	0.34
AST (U/L)	44.78 ± 31.27	44.48 ± 34.41	0.84
AFP (ng/ml)	3.75 ± 3.68	3.7 ± 3.8	0.19
Albumin (g/dL)	4.28 ± 0.44	4.24 ± 0.46	0.10
Total Bilirubin (mg/dL)	0.68 ± 0.73	0.67 ± 0.43	0.39
WBC (×10^3)	7.09 ± 4.86	7.31 ± 6.34	0.30
Hb (gm/dl)	13.66 ± 2.03	13.62 ± 1.77	0.34
Platelets (×10^3)	227.70 ± 85.5	226.85 ± 149.07	0.78
INR	1.10 ± 0.2	1.08 ± 0.14	0.13
Creatinine (mgdL)	0.94 ± 0.7	0.87 ± 0.53	0.33
HbA1c (%)	7.36 ± 7.98	6.29 ± 3.35	<0.01*
FIB-4	1.78 ± 3.50	1.80 ± 2.31	0.64
HCV_RNA_log10	5.64 ± 0.98	5.62 ± 0.92	0.59

*Statistically significant (≤0.05).

Results: Available results of 297,965 patients who underwent HBsAg testing showed that HBsAg was positive in 2,347 patients (0.8%). Patients with HBV/HCV; mean age: 51 ± 13 years, 57.1% females, and mean BMI 29.2 ± 7.6 kg/m^2 with. Tobacco consumption, IV drug abuse, hypertension and diabetes were more reported in HBsAg +ve patients ($p < 0.01$). HBsAg +ve patients showed less advanced fibrosis by FIB-4 ($p < 0.01$). Only 14% of those with HBsAg +ve had liver cirrhosis by ultrasound with 2 patients had HCC. HbA1c level showed

statistically significant difference between both groups ($p < 0.01$), being higher in HBV/HCV group. No significant difference in HCV viremia or FIB-4 score between patients with HCV mono infection versus HBV/HCV co-infection (P value = 0.592, 0.64) respectively (Table 1).
Conclusion: Although Egypt has heavy burden of HCV, yet, the overall prevalence of HBV/HCV co-infection is low among HCV-infected patients.

THU358
Risk of liver and non-liver-related mortality among hepatitis C virus and human immunodeficiency virus co-infected persons in a cohort of Brazilian blood donors: a twenty-year study
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Background and Aims: Hepatitis C virus (HCV) infection is a major health problem associated with an increased risk of morbidity and mortality. However, among HCV and human immunodeficiency virus (HIV) co-infected individuals, studies on of non-liver-related mortality have yielded inconsistent results. The purpose of this study was to investigate the contribution of HCV and HIV co-infection on liver and non-liver-related mortality, in a large cohort of blood donors in Brazil.
Method: This is a retrospective cohort study of blood donors from 1994 to 2013, at Fundação Pró-Sangue - Hemocentro de São Paulo (FPS). This cohort included 36 HCV and HIV antibody seropositive (HCV/HIV co-infected), 5,782 HCV and HIV antibody seronegative and 2,652 HCV antibody seropositive (HCV mono-infected) blood donors respectively. Records from the FPS database and the Mortality Information System (SIM: a national database in Brazil) were linked through a probabilistic record linkage (RL). Mortality outcomes were defined based on ICD-10 (10th International Statistical Classification of Diseases and Related Health Problems) codes listed as the cause of death on the death certificate. Hazard ratios (HRs) were estimated for outcomes using Cox multiple regression models.
Results: When all causes of death were considered, RL identified 14 deaths among HCV/HIV co-infected donors, 190 among HCV/HIV seronegative donors and 209 among HCV mono-infected donors. HCV/HIV coinfected donors had 6.63 times higher risk of death due to all causes when compared to HCV mono-infected donors (95% CI: 3.83–11.48; $p < 0.001$) and 14.57 times higher risk of death due to all causes when compared to seronegative donors (95% CI: 8.42–25.22; $p < 0.001$). When only liver-related causes of death were considered, RL identified 3 deaths among HCV/HIV coinfected donors, 6 among seronegative and 73 among HCV mono-infected. HCV/HIV coinfected donors had a 95.76 times higher risk of liver related death when compared to HCV/HIV seronegative donors (95% CI: 23.54–389.52; $p < 0.001$) and a 4.16 times higher risk of death when compared to HCV mono-infected donors (95% CI: 1.3–13.34; $p = 0.016$).
Conclusion: Our data suggests that among HCV/HIV coinfected blood donors, even after specific treatment and sustained virologic response, specific interventions are urgent and necessary, in order to avoid both liver and non-liver related complications and death.

THU359
Emergency department screening for hepatitis C carriers does not improve linkage to care - a single-center prospective study
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Background and Aims: Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease worldwide. New treatments for HCV revolutionized management and prompted the world health organization (WHO) to set the goal of viral elimination. To achieve this goal, better screening is needed, in order to identify asymptomatic carriers prior to development of chronic liver disease and its complications. Our aim was to identify HCV carriers among high risk emergency room attendees in order to link them to care and facilitate anti-viral treatment.
Method: Persons visiting the emergency department (ED) were screened for HCV by risk factor-specific questionnaire. Those with at least one risk factor were tested for HCV by serum for HCV antibodies, a novel oral test from saliva (OraQuick®) or both.
Results: Five hundred and forty-one participants had at least one risk factor and were tested for HCV. 3.1% (17/541) had a positive result as compared to the local population incidence of 1.96%. Of these, 82% were current or former intravenous drug users (IVDU), and 64% served time in prison. One patient had a negative HCV-PCR, and two patients died from non-HCV related reasons. At 1-year follow-up none of the remaining 14 patients had completed HCV-RNA testing, visited a hepatology clinic or received anti-viral treatment.
Conclusion: Targeted high-risk screening in the ED identified undiagnosed and untreated HCV carriers, but did not

	Univariate regression		logistic	Multivariate regression		logistic
Variable	Exp (b)	95% CI	P value	Exp (b)	95% CI	P value
Gender (female vs. male)	0.072	0.009-0.55	**0.011**	0.578	0.043-7.71	0.679
IVDU (yes vs. no)	402.889	91.3-1777.1	**<0.001**	188.95	33.88-1053.82	**<0.001**
Served time in prison (yes vs. no)	19.515	6.89-55.25	**<0.001**	4.076	0.623-26.67	0.143
HIV (yes vs. no)	17.6	4.8-64.6	**<0.001**	5.32	0.242-116.78	0.289
Born in the former USSR (yes vs. no)	0.25	0.09-0.67	**0.006**	0.562	0.092-3.42	0.532

Dependent variable – HCV positive. USSR - Union of Soviet Socialist Republics; IVDU - Intra-venous drug users.

Figure: (abstract: THU359) Multivariate analysis of risk factors for HCV

improve treatment rates. Other strategies need to be developed in order to improve linkage to care in high risk populations attending the ED.

THU360

Treating patients with DAAs helped to save €1 billion in France - a budget impact model from 2014 to 2018

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Background and Aims: New Direct Acting Antivirals (DAA) constituted a breakthrough innovation in chronic hepatitis C (CHC) treatments. Sustain virologic response rates (>90% vs 54%–70% previously) allowed cure in shorter treatment times with a fewer adverse events (AE) compared to treatment available prior to 2014. Studies have demonstrated new DAAs cost-effectiveness. With an estimated 72,000 patients treated in France from 2014 to 2018, this study assessed the economic impact of DAA launch.
Method: A budget impact (BI) model was constructed to estimate the BI of CHC between 2014 and 2018 and to extrapolate long-term (up to 40y) direct and indirect costs for treated CHC patients. Extrapolation was based on a Markov model that simulated the natural history of CHC. Real-world data was used for treatment patterns and patients' characteristics. Prices included published rebates and taxes. The model compared the real-world scenario (DAA) to a hypothetical scenario (no-DAA) where treatment patterns prior to 2014 were used for 2014–2018. No-DAA included lower number of treated patients and use of pegylated interferon, ribavirin, boceprevir and telaprevir only. Results compared direct costs (treatments, AEs, complications [HCC, decompensation, transplantation]) and indirect costs (loss of productivity) for both scenarios.
Results: Only 48,500 patients would have been treated in no-DAA between 2014 and 2018 compared to 72,000 with DAA with a respective treatment cost of 1 billion euros (B€) vs B€ 3.4. Long-term extrapolation shows an estimated B€ 1.9 vs 0.9 spending in other direct costs, and 2.4 in indirect costs for no-DAA; total cost was estimated to B€ 5.4 vs 4.3, over a billion saving for DAA.
Results will be provided regarding direct costs complications and deaths for the conference.
Conclusion: These results support that treating patients with DAAs will allow to save over a billion euros and was a good investment from a collective and patients perspective.

THU361

Outcomes of community and prison-based hepatitis C treatment using an eHealth model of care

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Background and Aims: eHealth technologies may provide a scalable, patient-centred model of care to address barriers preventing non-specialist initiation of direct-acting antiviral (DAA) therapy for chronic hepatitis C (CHC). In 2016, Australia introduced unrestricted access to DAA therapy allowing for prescription by any medical practitioner, however treatment rates have declined. We aimed to investigate the efficacy, acceptability and feasibility of an online eHealth system to connect community-based clinicians and patients with specialist teams for community and prison-based DAA treatment.
Method: A multicentre quasi-experimental pre-post study utilising a hybrid effectiveness-implementation design was conducted with referring community and prison-based clinicians in consultation with eight tertiary centres in Australia. The pre-intervention control group was treated through existing paper, fax or remote consultation methods between 1 March 2016–28 February 2017. The eHealth model of care (using the HealthElink system) was prospectively implemented from 1 August 2017–30 April 2019. Key elements of the web-based eHealth model include CHC specific clinical decision support (incorporating automatic calculation of drug interactions and fibrosis assessment), secure electronic messaging, task management, email alerts and a patient portal. The primary outcome was sustained virological response at twelve weeks following treatment (SVR12), including all subjects intended for treatment. Secondary outcomes include implementation analysis, usability, acceptability, safety and uptake measures.
Results: In total, 236 subjects (174 community, 62 prison) were treated in the eHealth group and 681 (588 community, 87 prison) in the control group. On interim analysis, 150/236 (64%) of the eHealth cohort have completed follow-up. Sixty-one general practitioners, 13 specialists, 17 nurses and 4 prison systems registered to use the eHealth system. To date, in the community-based group SVR12 was confirmed in 81/122 (66%) compared to 383/588 (65%) in the control group, and 21/28 (75%) v 61/87 (70%) in the prison-based group. Completion of repeat liver biochemistry at the time of SVR12 testing (89% v 56%) and adherence to guideline-based treatment (100 v 98%) were higher in the eHealth group.
Conclusion: An integrated, patient-centred eHealth model of shared care is feasible for chronic disease management and may improve clinical outcomes in CHC. We anticipate final results to be presented at the conference, incorporating further qualitative data and final results.

THU362

Testing and linkage to treatment programme for hepatitis C in different homeless locations in Greater Manchester, UK

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Background and Aims: Greater Manchester has a high prevalence of hepatitis C virus (HCV). There is a well-developed programme of clinics in prisons, Primary care, hospitals and Drug services but a significant amount of patients still do not engage.
Method: We started a test and treat programme in 3 different type of locations: emergency night shelters- "a bed for every night" programme (ABEN), homeless hostels (HH) and day centres (DC) for the homeless. All locations were visited by our secondary care team to provide testing in a limited number of sessions (2–4) by a 2

people team (a nurse and a HCW). Dried blood spot samples were tested for Anti-HCV and HCV RNA. The test use was a dry blood spot from Virology Department at Manchester NHS Foundation Trust with a sensitivity of 660 copies.

Results: Overall 114 patients were tested in this programme. Of those 71 (49%) reported substance misuse and 2 declined to answer. Six patients reported having previously been treated and cured with 1 of those being PCR positive (reinfection rate 20%). 28 of the total were antibody positive for HCV (25%) with 13 HCV PCR positive (11%). Excluding those 6 who received therapy 10 patients out of 22 (45%) were antibody positive and PCR negative.

Seven emergency centres from the Greater Manchester ABEN programme were visited 12 times in total with 44 patients tested. Six were antibody positive (2 had previous therapy) and 4 PCR positive for HCV (14% prevalence for Abs and 9% for PCR positive, one of those was a reinfection). Three patients were referred to treatment centres in drug services clinics (none attended) and 1 was treated (and cured) in the shelter.

Four hostels were visited 6 times in total with 29 patients tested. Six were antibody positive (one previously treated) and 2 PCR positive (21% prevalence for Abs and 7% for PCR positive). One patient was referred to a clinic at his GP practice and 1 is undergoing treatment in a hostel.

Two community centres were visited 7 times in total with 41 patients tested. Sixteen were found antibody positive (3 received previous therapy) and 7 PCR positive (prevalence 39% for antibody positive and 17% for PCR). Three patient have started therapy (one has completed), two did not come back to start and 2 are due to start within a week.

Conclusion: Emergency shelters and hostels have a relative low frequency of HCV PCR positive in Greater Manchester with the highest prevalence found in day centres although also with the lowest acceptability. This might be due to some degree of self-selection and might explain the higher prevalence in this setting. On going referrals to a treatment clinic is associated with lack of treatment initiation and it is not a valid strategy for this population, whilst local treatment works well when accepted, although in a day centre it is more difficult as patients use the facilities for a limited period of time and not always daily.

THU363

Achieving micro elimination of hepatitis C across a network of prisons in the north-west of England covered by a single treatment provider

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Background and Aims: Prisons are a critical part in the elimination of the hepatitis C virus (HCV). We provide HCV care for 6 prisons in the North West of England. In January 2018 the secondary care responsible for providing HCV therapy increased their workforce from 1 to 2 nurses and a health care worker to increase testing and faster treatment.

Method: Our network serves a population of around 4097 inmates. HMP Forest Bank (FB Male local prison - population 1501), HMP Manchester (M category A male- 933 males), HMP Lancaster Farms (LF category C male - 552), HMP Buckley Hall (BH category C Male-450), HMP Styal (S female - 446) and HMP Haverigg [H category C re-rolling currently to category D male – 215 (higher on the first year of network at 500+)]. Two prisons in the network take "on remand prisoners" (awaiting sentence): FB for males and S for females. These two prisons have a very large turnover of prisoners (3973 and 1430 new arrivals respectively in 2017).

Over a 12 month period this network had 9,980 new arrivals. All prisoners are offered testing when they arrive. This offer is then repeated usually once.

Besides this, secondary care nurses organised with the prison staff weekend testing events on the wings. Then target events for untested prisoners. Testing figures prior to the arrival of the extra secondary care staff and the testing events were- 2.5% for FB, 34% for M, 40% for LF, 56% for BH, 9% S, 56% for H. There were 251 referrals for therapy and 64 started therapy (25.5% of all referrals)

Results: In 2018 the secondary team provided 1137 (28% of total population) additional tests with 62 patients HCV PCR positive (5.5%). In 2019 (data to early November 2019) 1394 tests (34% of total population) were performed with 21 patients positive (1.5%).

Overall in October 2019 there were 410 prisoners declining a test out 4097 inmates (90% tested) whilst in November 2019 there were 261 out of 3871 inmates (93% tested). Three prisons achieved over 95% testing at both time points (BH 98 and 97% respectively, H 99 and 100%, LF 99% at both points). The other 3 prisons were above 80% at both points (M 81–93% respectively, FB 88–93% and S 92–81%).

In 2018 there were 391 referrals (56% increase) of whom 186 who started therapy (48% of all referrals) whilst in 2019 (to November) they were 342 referrals with 272 starting therapy (80%). During part of this period a HCV PCR Cepheid® machine was in use at HMP Styal allowing a rapid treatment start. Even if we exclude the 83 people tested through this project, we had 259 referrals with 193 starting on therapy (75% of referrals).

Conclusion: This project shows the success of supplementing prison testing efforts with special events to manage to test missing inmates to achieve microelimination (consistently testing of 90% of the inmates). Facilitating this with secondary care staff increases testing in this study but also increases very significantly patients starting on therapy whilst in prison.

THU365

Global timing of hepatitis C virus elimination in high-income countries: an updated analysis

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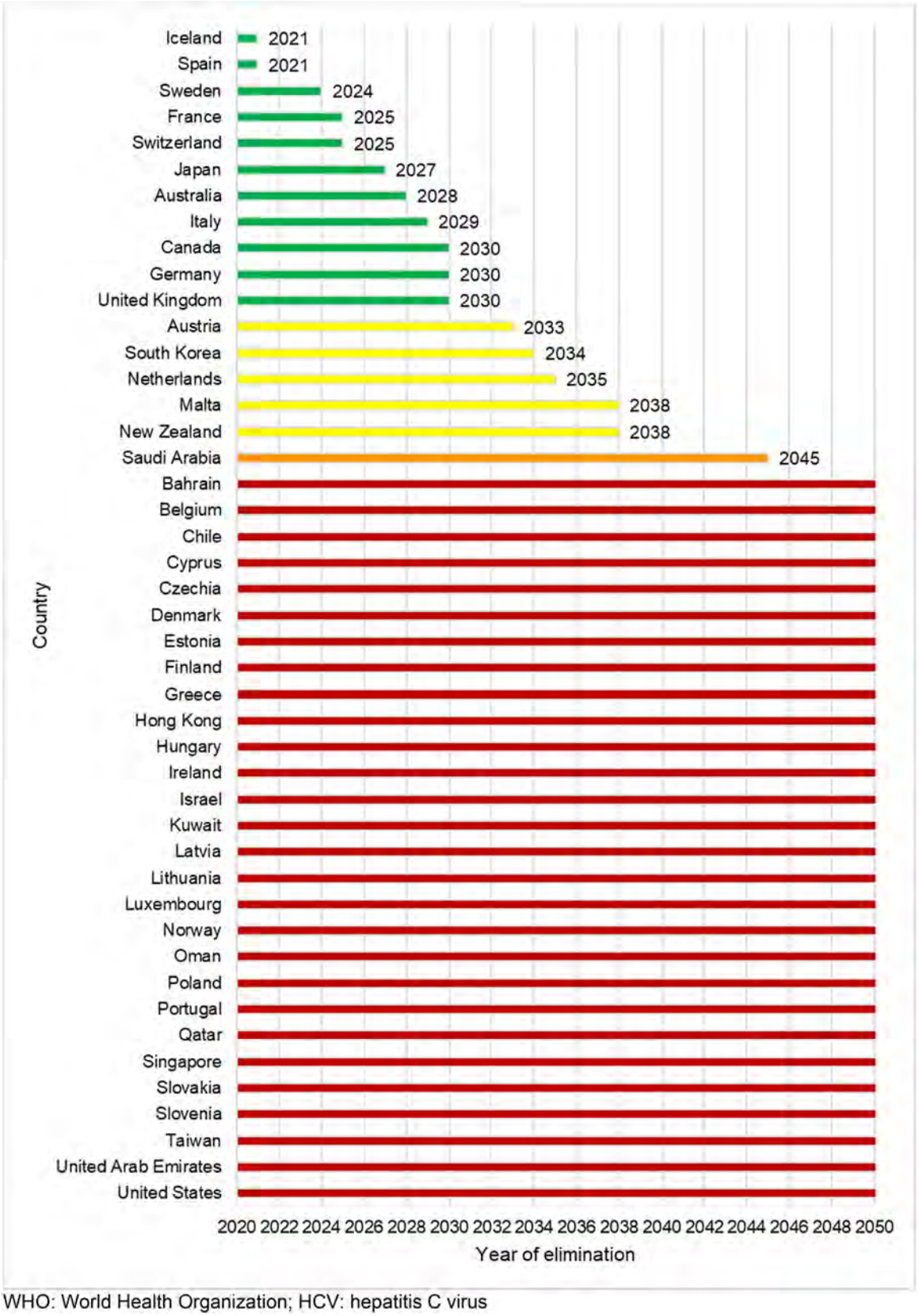
Background and Aims: Elimination of hepatitis C virus (HCV) by 2030 as set out by the World Health Organization (WHO) may be attainable with the availability of highly efficacious HCV therapies. This study updates a previously published analysis on the timing of HCV elimination in 45 high-income countries based on WHO's targets for incidence, mortality, diagnosis, and treatment.

Method: Previously published Markov disease progression models of HCV infection for 45 high-income countries were calibrated to the latest available data on chronic HCV prevalence, and updated with number of annual new diagnoses (with reported data over 2017–2018) and treatments (with reported and projected data over 2017–2019). The latest reported or projected levels of diagnosis and treatment were defined as baseline and optimistically assumed constant in the future. Modeled outcomes until 2050 were analyzed to determine the year in which each country would meet WHO's HCV elimination targets for reduction in incidence (80%) and mortality (65%), and diagnosis (90%) and treatment (80%) coverage relative to 2015 levels. Earliest year in which all targets were met was defined as the year of elimination.

Results: Of 45 high-income countries studied, 11 (Australia, Canada, France, Germany, Iceland, Italy, Japan, Spain, Sweden, Switzerland,



WHO: World Health Organization; HCV: hepatitis C virus

Figure: (abstract: THU365) Year of elimination per WHO's 2030 HCV elimination targets.

and the United Kingdom) are on track to meet WHO's HCV elimination targets by 2030; five (Austria, Malta, Netherlands, New Zealand, and South Korea) by 2040; and one (Saudi Arabia) by 2050. The remaining 28 countries are not expected to achieve HCV elimination before 2050. Of countries previously considered on track to eliminate HCV by 2030, one (South Korea) is now off track; of countries previously off track towards HCV elimination by 2030, three (Canada, Germany, and Sweden) are now on track. Most (29) countries saw no change since the previous analysis, with nine expecting an earlier time to HCV elimination, and seven expecting a later one. The incidence target, followed by mortality, remains the target fewer countries are expected to meet.

Conclusion: Assuming high-income countries will maintain their current levels of diagnosis and treatment, only 24% are on track to eliminate HCV by 2030 and 62% are off track by at least 20 years. If current levels of diagnosis and treatment continue falling, achieving WHO's 2030 targets will be even more challenging. With ten years remaining to meet these targets, expansion of screening and treatment is crucial to make HCV elimination possible.

THU366
Anticipated timing of elimination of hepatitis C virus in Canada's four most populous provinces

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Background and Aims: While direct-acting antiviral therapy for hepatitis C virus (HCV) infection has made HCV elimination an attainable goal, current diagnosis and treatment levels in many high-income countries are insufficient to reach World Health Organization's (WHO) 2030 elimination targets. This study examines timing of HCV elimination in Canada's four most populous provinces which account for 86% of total population.
Method: A previously published model of HCV progression was populated with reported data for Alberta (AB), British Columbia (BC), Ontario (ON), and Quebec (QC). For BC, chronic prevalence and diagnosis data from 2018, and average annual treatments over 2015–2018 were used. For AB, ON, and QC, prevalence and diagnosis data from 2007 and 2011, respectively, and peak number of treatments in Canada, prorated for each province, were used. As base case, diagnosis (from 2017) and treatment levels were assumed constant, optimistically, to determine year of achieving WHO's 2030 HCV elimination targets for reduction in incidence (80%) and mortality (65%), and diagnosis (90%) and treatment (80%) coverage. Impact of 5% and 10% annual reductions in diagnoses and treatments were explored as less optimistic scenarios. The minimum annual reduction in diagnoses and treatments for delaying HCV elimination beyond 2050 was also calculated.
Results: Under base case, BC would reach WHO's HCV elimination targets by 2028, ON by 2030, AB by 2031 and QC by 2035. At 5% annual reduction in diagnoses and treatments, BC would be on track to eliminate by 2030, AB and ON by 2040, and QC by 2050; at a 10% reduction, only BC and ON would eliminate by 2050. At 14% annual reduction in diagnoses and treatments, no province would eliminate HCV by 2050.
Conclusion: Assuming that current levels of diagnosis and treatment are maintained, only BC and ON are on track towards WHO's 2030 HCV elimination targets among Canada's four most populous provinces. With many of the currently diagnosed already being treated, increasing and maintaining diagnosis levels is critical for achieving the treatment levels that would make timely HCV elimination a reality in Canada.

THU367
Acute hepatitis C virus infection: a prospective ten-year observational study of HCV-mono and HCV/HIV-coinfected patients

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Background and Aims: An ongoing epidemic of acute hepatitis C (aHCV) infections has been observed in HIV-infected men who have sex with men (MSM) in several metropolitan areas worldwide. High SVR (sustained virologic response rates) have been reported in patients with acute hepatitis C using DAAs. However, repeated HCV infections have been observed in MSM after successful treatment. This study aimed to investigate parameters of epidemiological, clinical and phylogenetic evolution of acute hepatitis C over a time period of ten years.
Method: In this prospective, ongoing observational study, n = 167 patients with acute hepatitis C infection were included at three centers in Frankfurt between 2009–2019. Thereof, n = 24 were HCV monoinfected and n = 143 had a HCV/HIV coinfection (MSM).
Results: During the first 5 study years, the prevalence of HCV genotypes (GT) was: GT1a, 72% (n = 76/106); GT1b, 7% (n = 7/106); GT2, 3% (n = 3/106); GT3, 4% (n = 4/106); GT4, 12% (n = 13/106) and GT undetermined, 3% (n = 3/106). However, during the last 5 years higher frequencies of GT4 infections (20%, n = 12/61) were detected, while GT1a (77%, n = 47/61) and GT3a (3%, n = 2/61) infections stayed stable and no GT1b or GT2 infections were observed. The overall number of patients annually included decreased during the

Province	Anticipated year of HCV elimination			Annual treatments needed over 2020–2030 for HCV elimination by 2030
	Base case (0% reduction*)	5% reduction*	10% reduction*	
Alberta	2031	2035	-	1,300
British Columbia	2028	2030	2033	3,900
Ontario	2030	2033	2044	5,300
Quebec	2035	2043	-	2,100

* Reduction in HCV screening and treatment
- No HCV elimination before 2050

Figure: (abstract: THU366) Progress towards HCV elimination targets

last 5 study years (Figure 1). Spontaneous clearances rates were higher in HCV-mono- compared to HCV/HIV-coinfected patients (37%, n = 7/19 versus 13%, n = 18/135 patients with follow-up (FU) data available). Out of the initial population, 65% (n = 109/167) had completed antiviral treatment and FU. The median time between aHCV diagnosis and treatment initiation was 23.6 weeks. Overall, n = 60 individuals were treated with pegylated-interferon/ribavirin (P/R) with or without a direct acting antiviral (DAA). Further n = 49 patients received an interferon-free DAA treatment and all achieved SVR. The only two virologic failures observed had failed to P/R. During the 10 years observation period, n = 27/167 (16%) HCV/HIV-coinfected patients had acquired one or multiple acute HCV reinfections after spontaneous clearance of initial infection or achievement of SVR.

Conclusion: During the last 5 study years the prevalence of GT4 infections increased, while annual acute hepatitis C incidences decreased. Spontaneous clearance rates were higher in HCV-mono- compared to HCV/HIV-coinfected patients. Overall, 16% of HCV/HIV-coinfected patients had a HCV reinfection which may have implications for HCV elimination in MSM.

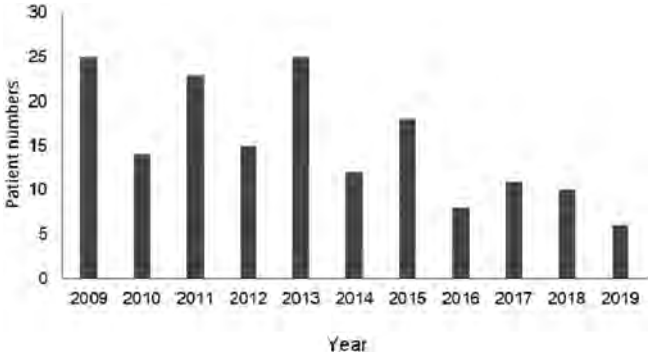

Figure 1: Numbers of patients annually included.

THU368

Improving the referral of hepatitis C virus positive patients to specialists through an electronic "pop-up" alert system

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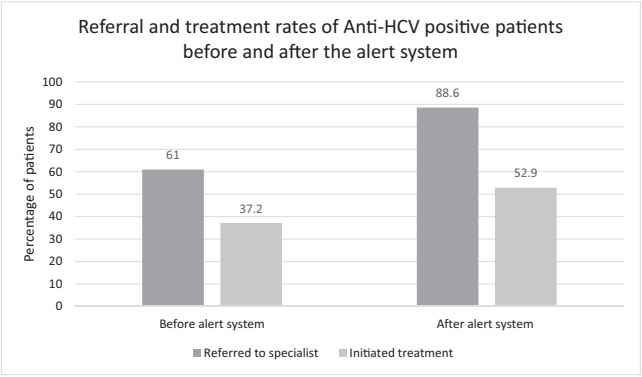
Background and Aims: Hepatitis C virus screening tests are often ordered as a part of medical check-up, preoperative or before transfusion. However, patients with Anti- HCV positive results are not sufficiently referred to specialists to receive treatment or for follow-up. Direct-acting antivirals (DAAs) offer a highly effective treatment response in short periods and it leads to decreased morbidity and mortality due to HCV infection. We introduced a simple "pop-up" alert system to increase the referral of Anti-HCV positive patients to gastroenterologists or infectious disease specialist through their electronic medical records. We investigated referral rates to specialists before and after the introduction of the "pop-up" alert system.

Method: From an area representing approximately 3 million population in Istanbul (North Anatolian Side), 5 reference and 7 district hospital medical records were searched for Anti-HCV and HCV RNA positivity. The referral rate to specialists was compared before (from January 2014 to January 2018) and after the introduction of the "pop-up" alert system (from January 2018 to May 2019). The "pop-up" alert system has been automatically integrated to the hospital electronic health records and it appears whenever the patients' medical records are viewed. It is activated with the positive Anti-HCV results and contains a comment to the physician for referral of the patient to a specialist.



Results: From January 2014 to May 2019 Anti-HCV antibody was tested in 601832 patients. Of these, 7410 (1.2%) patients were found to have positive Anti-HCV, and 1775 (0.29%) patients had positive HCV RNA. The referral rate to gastroenterologists after the "pop-up" alert system has improved from 61% to 88.6% and patients who received treatment increased from 37.2% to 52.9%. Admission to a specialist as an in-patient or immediately after discharge increased from 21.8% to 54.6%.

Conclusion: The electronic "pop-up" alert system increased the referral and treatment rates of patients with HCV. This approach could be an important strategy to detect and treat patients with chronic HCV infection.

THU369

Predictors of disengagement or delay after hepatitis C assessment

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Background and Aims: Models of hepatitis C elimination in the directly-acting antiviral (DAA) era often assume that patients will progress to cure after assessment with minimal attrition or delay. We aimed to quantify disengagement or delay between assessment and treatment and determine the patient- and pathway-based factors that predict them.

Method: We analysed a cohort of 2762 patients assessed and approved for DAA treatment in North Central London between July 2014 and March 2019. A bespoke patient management system allowed quantitative attribution of any delay to patient or system factors. Multivariate analysis of disengaged versus treated (or delayed versus non-delayed) cohorts was performed against a number of patient, disease and setting characteristics.

Results: A total of 197 patients (7.1%) have not progressed to treatment, of which 90 have disengaged. Of 2565 treated patients, 517 (20%) had pre-treatment patient-attributable delays that exceeded treatment duration and in 206 (8%) this delay exceeded 6 months. Multivariate analysis revealed that those assessed in prisons had the highest risk of disengagement before treatment (OR 11.9, 95% CI 5.9–23.79, $p < 0.0001$). In all settings, UK-born patients had a 2-fold increased risk of disengagement compared with non-UK born (OR 1.95, CI 1.121–3.391, $p = 0.018$) and HIV positive patients were 7.8 times less likely to disengage before treatment (OR 0.128, CI 0.03–0.544, $p = 0.006$). Gender, injected drug use (IDU), treatment experience, excess alcohol or treatment in community drug services had no significant impact on disengagement risk after assessment. However, in the treated cohort, delays >6 months were more likely to be incurred by those with a history of IDU (OR 1.62, CI 1.1.6–2.256, $p = 0.005$).

Conclusion: Prisoners and those with a history of IDU have high onward transmission risks which are exacerbated by their greater likelihood of disengagement and delay after assessment. In all settings, multiple patient factors can predict progress arrest and

these may guide targeted preventative interventions. However, these account for the minority of variation in patient behaviour in this model (Nagelkerke R square = 0.17). Qualitative research examining patient motivation, knowledge, skills and opportunities may better predict and prevent disengagement.

THU370

Predictors of workload in a hepatitis C treatment pathway

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Background and Aims: The workload of treatment pathways for hepatitis C is determined not only by caseload but also the number of contacts required per patient to plan and monitor treatment. Progress towards elimination will require agile and efficient pathways that can allocate resources according to predicted individual need. We aimed to identify factors that significantly impact the pathway workload from assessment to end of treatment.
Method: We analysed a cohort of 1499 patients undergoing directly-acting antiviral (DAA) treatment in North Central London between April 2016 and April 2019. These patients were managed using a bespoke system which allowed quantitative attribution of any pathway progress delay to patient or system factors. Pathway workload (PW) was calculated as the total number of pathway coordinator (PC) contacts and treatment monitoring (TM) encounters recorded between approval for treatment and end of treatment for each patient. Multivariate linear regression analysis was used to determine if specific patient, disease and setting factors independently correlated with PW.
Results: A mean of 2.72 (95% CI 2.587–2.848) PC contacts and 9.1 (CI 8.89–9.30) TM encounters were required between treatment approval and end of treatment. PW was positively correlated with patient factors including patient-attributable delay (B = 0.021, CI 0.019–0.022, p < 0.0001), ex or current intravenous drug use (B = 0.722, CI 0.246–1.197, p = 0.003) and age (B = 0.033, CI 0.016–0.051, p < 0.0001) and disease factors including cirrhosis (B = 2.141, CI 1.552–2.731, p < 0.0001), post-liver transplant (B = 1.933, CI 0.532–3.334, p = 0.007 and ribavarin-inclusive treatment (B = 1.789, CI 1.305–2.272, p < 0.0001). HIV positive patients required significantly fewer contacts/encounters (B = –4.252, CI – 5.064–3.440, p < 0.0001), as did patients monitored in prisons (B = –5.4,CI –7.9–2.9, p < 0.0001) or community drug services (B = –1.3, CI –2.591–0.044, p = 0.04).
Conclusion: These data demonstrate the significant impact of poorly-engaged patients on increased pathway workload (Figure 1) and would justify pre-emptive interventions to reduce patient-attributable delay or disengagement. Incorporating hepatitis C treatment into existing care pathways (e.g. HIV treatment, drug addiction services) with which patients are already well-engaged significantly reduces pathway workload.

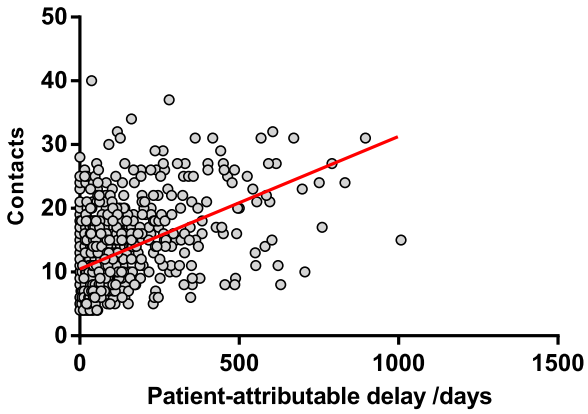

Figure: Patient delay and pathway workload.

THU371

Micro-elimination of hepatitis C in mental health care settings

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Background and Aims: Marginalised populations including people with mental illness are disproportionally affected by chronic hepatitis C (CHC). The estimated prevalence of CHC in Western Sydney is 0.81%. Among people with mental illness, ~50% population report a history of substance misuse, 14% having injected drugs and half admit to sharing injecting equipment. We sought to achieve inpatient and community mental health CHC micro-elimination in Western Sydney, Australia.
Method: Systematic screening was introduced across 9 community mental health teams and 1 inpatient psychiatric facility. Testing was offered to all clients, partnered with harm reduction and education delivered by study specific nurses and appropriately trained mental health nurses. Patients who had viremia progressed to clinical assessment, case discussion and treatment. Nurse led end of treatment and 12 weeks post assessment was undertaken. Screening and treatment was delivered in the mental health setting.
Results: To date, 640 patients have been screened, 46% (n = 294) were inpatients while 54% (n = 346) were within the community mental health setting. During the latter half of the project, the availability of a pathology collector at community clinics reduced the time between initial contact and blood collection and increased likelihood of consent to testing.
Of the 294 inpatients and 346 community patients, 7.4% (n = 22) and 3.1% (n = 11) respectively, were found to be hepatitis C virus PCR positive. Ten inpatients commenced treatment; 3 achieved a sustained virological response (SVR), 6 are awaiting week 12 results and there was 1 treatment failure. Five others are awaiting treatment, 3 were discharged and require further follow up, and 4 refused treatment. Of the 11 patients assessed for treatment within the community setting, 3 commenced treatment; 2 completed and await SVR and 1 continues on treatment. Of the remaining 8, 6 refused treatment, 1 spontaneously cleared, and 1 patient was diagnosed with hepatocellular carcinoma and referred for further investigations and treatment, their CHC treatment was deferred.
Conclusion: CHC prevalence rates are higher in mental health settings compared to the overall population. Collaborating with and educating stakeholders across the mental healthcare sector resulted in significant numbers of patients being screened for CHC. Screening likelihood increased when venipuncture was offered at initial contact. While treatment uptake remains a challenge, with appropriate support, progress toward treatment initiation is achievable.

THU372

Triple E (engagement, education and eradication) for patients with chronic hepatitis C infection: >2 years of results of a successful, collaborative US model for improving education, screening and linkage to care in an underserved population

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Background and Aims: The United States (US) opioid epidemic has led to increases in hepatitis C viral (HCV) infections. Despite HCV being recognized as prevalent in individuals with substance use disorders (SUDs), the vast majority of substance abuse treatment facilities in the US do not screen for HCV. Lack of clinical staff and/or access to knowledgeable HCV experts' limits screening and disease management.
In 2017 the Chronic Liver Disease Foundation (CLDF), a non-profit educational organization dedicated to increasing awareness of the effects of chronic liver disease in the US, designed and implemented an integrated HCV program to improve the care of individuals with SUDs.
Method: This program provided 4 fundamentals to substance abuse centers: staff education, patient education/counselling, antibody (Ab) screening/HCV RNA testing (if Ab positive) and linkage to care. Linkage to care linked HCV RNA positive individuals directly to hepatitis specialists onsite or via telemedicine in areas where HCV providers are limited. A CLDF healthcare counsellor or local collaboration expert was involved in on-site patient education. Screening and linkage to care data were measured and the results of over two years of data are reported here.
Results: This began with substance abuse centers in 3 states and expanded to 8 states. Results from a smaller cohort were reported at EASL 2019. Results from a larger cohort are summarized here. Overall, 1131/2713 (42%) of SUD individuals, unaware of their HCV status, tested positive for HCV Ab. Of the 825 HCV Ab positive individuals who were tested for HCV RNA, 67% (552/825) tested positive. Some individuals could not complete a blood draw for various reasons and were referred for further confirmatory testing opportunities.
Conclusion: Direct-acting antiviral drug regimens offer the possibility of eradication of HCV but patient and provider HCV education, screening and linkage to care are necessary to effectively integrate treatments into disease management. Extending this program for an additional year resulted in substantially more patients who are now aware of their HCV status and have been effectively linked to care. Further broadening the reach of this self-sustaining, comprehensive HCV education, screening and treatment model could result in recovery center-focused eradication of HCV. This will have an invaluable effect on public health. This initiative was supported by educational grants from AbbVie and Gilead Sciences.

THU373

Prevalence of hepatitis C in a gastrointestinal endoscopy unit. An active search for asymptomatic subjects

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Background: A national cross-sectional, population-based survey carried out in Spain recently estimated HCV seroprevalence (0.85%) and viremia prevalence (0.22%) in the general population. The identification of asymptomatic subjects allows establishment of effective treatment and contributes to the elimination of the disease.
Aims: 1) To estimate seroprevalence and prevalence of HCV infection in a gastrointestinal endoscopy unit of a public hospital in Spain. 2) To describe epidemiological characteristics and known risk factors of HCV infection. 3) To asses acceptance and feasibility of an HCV screening program in a digestive endoscopy unit.
Method: Design: Observational, cross-sectional study.

- Population: All consecutive patients attended in the Gastrointestinal Endoscopy Unit between February and October 2019.
- Variables: 1) outcome: HCV serology, HCV viremia and genotype. 2) descriptive: id number, age, sex, nationality, known risk factors for HCV infection.
- Data collection: all subjects were invited to participate and sign in the study informed consent form. Information on descriptive variables was obtained from the Valencian Health Service database. An epidemiological survey was performed to all the participants were HCV risk factors were collected.

  HCV serology was obtained using a rapid anti-HCV finger stick blood test (Core HCV) amongst those who agreed to participate. An attempt to determine HCV viremia and genotype was done using PCR in seropositive subjects. All anti-HCV positive subjects were evaluated through personal interviews where clinical and analytical data were collected. Liver assessment of all anti-HCV positive subjects was carried out using abdomen ultrasound and transitional elastography.

Results: Anti-HCV test were performed in 3395 out of 3462 subjects invited to participate (98.1%) who underwent the following explorations: colonoscopy 1643, upper endoscopy 1373, both 314, ERCP 65. In all, 68 subjects (mean age 58, range: 38–85) were anti-HCV positive, resulting in an estimated prevalence of 2% (95%CI: 1.53%–2.47%). Of those, 11 were not aware of their condition and 64 (94%) reported one or more HCV risk factors. 12 subjects showed positive RNA-VHC viremia, with an HCV infection prevalence of 0.35%. 56 anti-HCV positive subjects (82.3%) were born between 1950 and 1979.
Conclusions: 1. The anti-HCV seroprevalence in the gastrointestinal endoscopy unit was 2%, higher than that reported in general population in Spain but HCV infection prevalence (0.35%) was similar. 2. Most anti-HCV positive patients were born in 1950 to 1979. 3. The majority of anti-HCV positive subjects were aware of this condition and had one or more HCV risk factors. 4. Digestive endoscopy units may be suitable areas for HCV screening.

THU374

Why didn't I see you in my clinic? Patients with HCV positive serology but never a confirmed infection. A retrospective analysis at 10 years

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Background and Aims: Although it is estimated that 29.4% of patients with active infection in Spain are unaware of their situation, there are few data on the profile of patients with positive serology but not well established viral status. Our aims was to evaluate the epidemiological and clinical profile of patients with positive HCV serology (HCVAb+) in our hospital, with special interest in patients without subsequent microbiological confirmation.
Method: Descriptive cross-sectional study on all those patients who presented any non-negative HCVAb serology between the years 2008–2017. After approval in the Ethics Committee, the patients were subclassified according to analytical evolution and the clinical digital reports.
Results: 14496 analytical codes containing "non-negative" HCV were extracted, after which analysis allowed to identify 2012 patients HCVAb+, 282 of whom had no RNA determination. Of these, 184 patients (65.2%) came from Primary Care (PC) and 98, from hospital and attached centers (mental health and drug dependence center). Among the patients from PC, 123 were not referred by their General Practitioner (66.8%) and 61 (33.2%) were, although they did not go to the specialist. The platelet count <150 × 109/L (60% referred vs. 30.6% not, p = 0.009) and ALT > = 35U/L (42.5% referred vs. 25.9% not, p = 0.021) were associated with higher referral rate to the Hepatologist. Among the patients who did not come from PC, most of the serologies were requested by Internal Medicine (30.6%), followed by General

Gastroenterology (23.5%) and Pneumology (14.3%), as shown in Table 2. 36 of 98 patients (36.7%) were referred, of whom 28 attended the consultation (77.7% of the derivatives) but none of them extracted the analytical with RNA requested from specialist. The only variable associated with the derivation rate was the origin of Gastroenterologist vs. other specialties (p = 0.014). Platelets <150 × 109/L and alcohol consumption >30gr/d were not related with higher referral but were close to statistical significance (p = 0.069 and p = 0.097, respectively).

Conclusion: Of the patients HCVAb+ who have not confirmed active HCV infection, approximately 2/3 are subjects who were not referred by the serology petitioner. In the case of Primary Care, thrombocytopenia and hypertransaminasemia are variables associated with a greater referral rate. In the rest of sources, only the origin of the analytical request was related with the appropriate derivation (greater if the petitioner was Gastroenterologist).

Variable		Primary Care (n=184)	Not Primary Care (n=98)	*P value*
Sex n(%)	Male	128 (69,6%)	71 (72,4%)	*ns*
	Female	56 (30,4%)	27 (27,6%)	
Age (years)		50,3 (±12,1)	49,1 (±14,4)	*ns*
Origin n(%)	Spain	79 (42,9%)	75 (76,5%)	*0,000*
	No data	46 (25,0%)	1 (1,0%)	*0,000*
	SubSahara	24 (13,0%)	6 (6,1%)	*ns*
	East Europe	22 (12,0%)	10 (10,2%)	*ns*
	Maghreb	9 (4,9%)	2 (2,0%)	*ns*
	Others	4 (2,2%)	4 (4,1%)	*ns*
Alcohol n(%)	<30gr/d	23 (12,5%)	41 (41,8%)	*ns*
	≥30gr/d	21 (11,4%)	31 (31,6%)	
Ex-IDUs n(%)		47 (25,5%)	26 (26,5%)	*ns*
Active DU n(%)		11 (6,0%)	21 (21,4%)	*0,000*
Died n(%)		21 (11,4%)	27 (27,6%)	*0,000*
Risky sexual behaviour n(%)		4 (2,2%)	7 (7,1%)	*ns*
Psychiatric disorders n(%)		35 (19,0%)	27 (27,6%)	*ns*
Previous transfusion n(%)		1 (0,5%)	13 (13,3%)	*0,000*
HBV or HIV Co-infectión n(%)		50 (27,2%)	18 (18,4%)	*ns*
Other Liver disease n(%)		21 (11,4%)	29 (29,6%)	*0,000*
Kidney disease n(%)		6 (3,3%)	6 (6,1%)	*ns*
ALT≥35U/L n(%)		87 (47,3%)	59 (60,2%)	*0,038*
Platelets <150x10^9/L n(%)		20 (10,9%)	20 (20,4%)	*0,028*
Referral to specialist n(%)		61 (33,2%)	36 (36,7%)	*ns*

Table 2

Petitioner Department	Value (n=98)	Derivation n(%)
Internal Medicine	30	9 (30,0%)
Gastroenterology	23	17 (73,9%)
Pneumology	14	4 (28,6%)
Dermatology	6	2 (33,3%)
Psychiatry	6	0 (0%)
Gynecology	4	0 (0%)
Drug Dependence Center	3	1 (33,3%)
Others	8	1 (12,5%)
No data	4	2 (50,0%)

THU375

Timing of hepatitis C elimination in the United States: estimating the year each state will meet the World Health Organization's elimination targets

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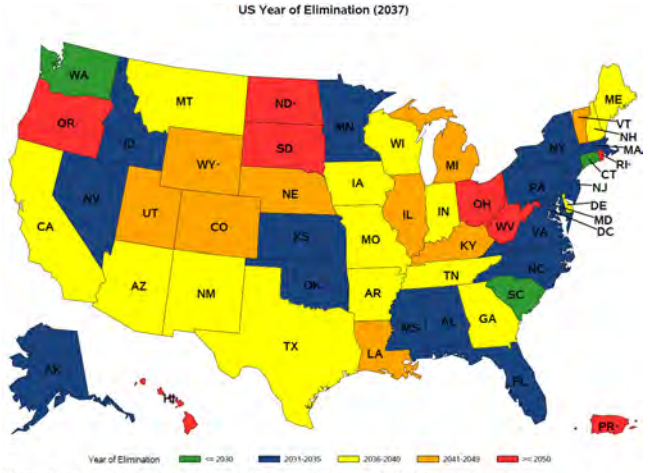
Background and Aims: Short-duration, pan-genotypic curative therapies can accelerate the path to HCV elimination. This study assesses the progress and timeline of US states to achieve the 2030 HCV elimination targets set by the World Health Organization (WHO) for incidence, mortality, diagnosis, and treatment.

Method: A previously published disease-progression model was utilized to project the path to HCV elimination based on national and state-specific population, mortality, and HCV prevalence statistics. Data from two US large laboratory companies were used to estimate HCV prevalence from 2013 to 2017, including the diagnosed HCV population, newly diagnosed HCV cases and number of patients receiving antiviral treatments in 2017. Fibrosis-stage restrictions for treatment reported in 2017 for each state were also considered. The model then estimated the annual HCV-infected population by stage of liver disease, and HCV-related deaths. To inform the path towards HCV elimination, the model estimated the year each state would meet the WHO targets for: diagnosing 90% of the HCV-infected population; treating 80% of the eligible population; and reducing new HCV infections by 80% and HCV-related deaths by 65% relative to 2015 benchmark levels. We also calculated the minimum number of annual treatments necessary to achieve the treatment target for HCV elimination, over the course of 2020 to 2030.

Results: Overall in the US, the estimated year of achieving WHO elimination targets is 2037, with 2037 being the year the target for incidence reduction will be met, 2020 for reducing liver-related mortality, 2027 for diagnosis coverage and 2033 for treatment coverage. Only three of 50 states (Connecticut, South Carolina and Washington State, 6%) are on track to eliminate HCV by 2030. An additional 16 states (32%) were projected to eliminate HCV by 2035, 15 (30%) by 2040, 10 (20%) by 2050, and 8 (16%; Hawaii, North Dakota, Ohio, Oregon, Puerto Rico, Rhode Island, South Dakota, and West Virginia) not before 2050.



*The estimation might be less accurate due to small number of HCV patients in the area

Conclusion: Our study suggests that the US is not on track to meet the WHO goals for HCV elimination by 2030 since only 6% of states are on track and 36% are off track by 10 years or more. As the year when all US states are expected to achieve HCV elimination targets is beyond 2050, strategies must be implemented to reduce HCV incidence, which include increased rates of screening, linkage to care, and unfettered access to curative therapy.

THU376

Managing hepatitis C in people who inject drugs (PWID) using the internist-addiction medicine-hepatology (IAHC) model to achieve Hep C micro-elimination

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Background and Aims: 2.5 million people in the United States are living with hepatitis C (HCV) with 80% of new infections occurring among People Who Inject Drugs (PWID). Rates of acute HCV among

people age 18–29 have increased 400%. In order to achieve the World Health Organization's target to eliminate HCV by 2030 improved screening, linkage to care and treatment among PWID is essential. This study describes the internist- addiction medicine-hepatology colocalization model (IAHC), an integrated, co-located program in which an internist-addiction medicine specialist evaluated opiate dependent patients for HCV infection in the hepatology clinic.

Method: Our clinic site applied the IAHC model to target PWIDs with HCV by partnering with community substance abuse clinics. Each site was educated on HCV screening and IAHC based social workers rotated among the referral sites on a weekly basis. The social work team collected the referrals, scheduled patients within thirty days and delivered the appointments directly to the referral sites the following week. The social work team remained in close contact with patients and provided weekly reminders as well as a call the day prior to the appointment. Upon being seen in the hepatology clinic, patients underwent HCV evaluation and medication-assisted treatment (MAT) for opiate dependency was offered if the patients were not already on therapy.

Results: 321 PWID were evaluated for HCV. 258 individuals completed direct acting antiviral (DAA) therapy of whom 168 achieved SVR (98.8%). 96 patients remain on treatment. 45 individuals failed to complete therapy due to various reasons, 4 had spontaneous resolution, 4 were unable to get treatment (pregnant, drug interactions, insurance issues). Overall adherence among PWID was 85.4%. 5 re-infected patients were identified and retreated.

Out of 379 general population, non-PWID patients who initiated HCV treatment, 236 completed treatment and 55 remain on therapy. 88 failed to complete treatment (incarcerated, insurance lapse, deceased, side effects, lost to care). Overall adherence was 73%.

We compared adherence amongst patient in the IAHC model (175/205) vs adherence in the regular model (236/324) and upon calculating the Chi-Square analysis, X2 = 5.71 and p-value was 0.016 which is clinically significant. The IAHC model was found to result in improved adherence.

Conclusion: The IAHC model of care is an effective strategy for HCV micro-elimination resulting in improved treatment uptake among PWID and high SVR rates. Early treatment of HCV can also result in increased treatment uptake for opiate dependency.

THU377

Testing and treatment for hepatitis C in the community pharmacy setting: an opportunity not to be missed?

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Background and Aims: To deliver against the World Health Organisation (WHO) Hepatitis C elimination agenda it is vital that services are developed that enable clients in high prevalence settings to be diagnosed and treated in an environment that is convenient and appropriate for them. This project was developed to investigate whether testing and treating clients for hepatitis C was feasible and successful in a community pharmacy setting.

Method: A national service specification acceptable to all pharmacies across Wales was agreed. Pharmacies with a high turnover of clients using enhanced services; needle exchange and opiate substitution therapy (OST) were approached to take part in the project. Pharmacy staff were trained on site in carrying out consent and dried blood spot testing (DBST) and all clients attending for enhanced services were offered DBST. 16 pharmacies across 3 Health Boards were enrolled. Positive results were followed up with a visit by a member of the liver team and treatment was subsequently prescribed in line with the All Wales guidelines.

Results: 500 clients were approached. 56 (11%) agreed to a test. The uptake of testing was much lower than anticipated, seemingly driven by 2 linked factors: a reluctance amongst the clients to accept the offer of a test (requests sometimes met with aggressive refusals) resulting in hesitancy amongst pharmacy staff to offer the test. Of the first 130 clients approached reasons for declining the test were given as no time (41%), no incentive to take the test (18%) and recently tested (41%). Of the 56 clients tested, 16 tested antibody positive on DBST with 4 testing RNA positive. Details of the barriers in testing that were encountered will be explored in the poster.

Conclusion: Uptake of testing in the community pharmacy setting was very low. The project experienced a number of unexpected barriers to testing. Alternative methods for enhancing engagement are needed to increase testing uptake in this setting. Ongoing education for pharmacy staff is also vital. Despite the disappointing uptake of testing, the interactions with pharmacy teams has been positive with increased awareness and understanding of the blood borne viruses. Development of the testing pathway in this setting continues as approximately 50% of at risk clients only access community pharmacy services. In rural areas delivery of treatment in this setting is likely to be crucial in achieving the WHO elimination targets.

THU378

Hepatitis C virus antigen detection as a tool for diagnosis of acute hepatitis C in patients with negative hepatitis C virus antibody

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Background and Aims: World Health Organisation has named the elimination of Hepatitis C virus (HCV) as one of its key goals; hence early diagnosis remains key for effective prevention and treatment. Current HCV antibody (Ab) tests as a screening tool has limited utility in acute Hepatitis C, especially in subjects who are immunocompromised. As HCV antigen (Ag) can be useful in this clinical scenario, this study is aimed to study utility of HCV Ag testing as a screening tool.

Method: This study cohort comprises of nineteen samples from patients with acute hepatitis C who were HCV Ab negative, but HCV RNA positive and eighty-nine subjects who have been treated or having chronic Hepatitis C were all checked for HCV Ag.

The Abbott ARCHITECT HCV Ag assay Abbott architect kit was used to check test for the presence of HCV antigen Ag a, value of >3.00 fmol/L was considered as positive. HCV titre was measured by real-time quantitative PCR from Roche COBAS® AmpliPrep/COBAS® Taqman® HCV Quantitative Test v2.0.

Results: HCV Ag was positive in 19/19 plasma of subjects with acute HCV who had detectable HCV RNA, but not HCV Ab. In the plasma of 44 subjects with HCV RNA positive - HCV Ag was positive in 43/44 subjects. In the patients who had treated HCV with HCV Ab positive and HCV RNA negative, the HCV Ag was negative in all the 37 subjects

Conclusion: HCV Antigen is useful for diagnosis of acute hepatitis C infection with shorter turn over time. This is especially useful in patients on hemodialysis or who are immunocompromised where the utility of HCV Ab test is limited.

Characteristics of Acute HCV infection

Subjects with Acute HCV

	HCV RNA positive	HCV Ab detected
HCV Antigen positive	19	0

Subjects with chronic HCV, HCV Ab and HCV RNA positive

	HCV RNA positive
HCV antigen positive	43
HCV Antigen negative	1

Patient with negative HCVAntigen test had HCV RNA of 3049 IU/ml

Subjects with treated HCV , HCV Ab positive and RNA negative

	HCV RNA negative
HCV Antigen positive	0
HCV Antigen negative	37

Figure: (abstract: THU378)

THU379

Screening for chronic liver diseases in the general population reveals an unexpectedly high prevalence of hepatitis C and advanced NAFLD

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Background and Aims: Hepatitis C virus (HCV) infection and non-alcoholic fatty liver disease (NAFLD) are common causes for chronic liver disease and are associated with an increased risk for advanced liver disease as well as cardiovascular disease (CVD). Data on the prevalence of liver diseases such as chronic viral hepatitis or fatty liver disease in particular are limited. The cost-effectiveness of population-based HCV screening to achieve WHO goals for eradication of HCV infection is under debate. Here, we provide preliminary data of a population-based combined Hepatitis C and NAFLD screening program in Austria.

Method: As part of a colorectal carcinoma colonoscopy screening program (SAKKOPI), we investigated 661 asymptomatic subjects (median age 58.8 years [53.3–64.4], 56% males). The diagnosis of fatty liver disease was established by abdominal ultrasound and transient elastography-based controlled attenuation parameter (CAP) ≥ 280 dB/m after exclusion of autoimmune or hereditary liver diseases, excess alcohol consumption and previously diagnosed viral hepatitis. Assessment of fibrosis using transient elastography (≥7 kPa for significant fibrosis [≥F2] and ≥ 10 kPa for cirrhosis [F4]) as well as biochemical and metabolic parameters, including liver enzymes, oral glucose tolerance test, insulin resistance (HOMA-IR) and HbA1c was performed. In addition, a detailed questionnaire of dietary habits and physical activity was completed. If serologic testing was positive for HCV antibodies, HCV infection was confirmed by PCR.

Results: In 661 patients, median BMI was 25.9 (23.4–29.0). 200 patients (30%) had elevated liver enzymes (GGT/ALT) and 246 (37%) had (pre-) diabetes. Mean Fib4 score was 1.07; 527 patients (80%) had Fib4 scores <1.45, while 123 (19%) and 11 (2%) had scores between 1.45–3.25 and >3.25 (indicative for advanced fibrosis), respectively. 42% of patients showed increased echogenicity on ultrasound examination. On transient elastography, mean CAP-value was 265 dB/m (221–311), whereas 269 (42%) patients had CAP-values above 280 dB/m. 63 (10%) of NAFLD patients had significant fibrosis (≥F2) and 16 (2.5%) had liver cirrhosis.

Furthermore, 6 patients (0.9%) had detectable HCV antibodies. 5 of them (0.8%) had chronic HCV infection confirmed. Notably, two patients with chronic HCV infection had completely normal laboratory, ultrasound and transient elastography findings.

Conclusion: We show an unexpectedly high prevalence of chronic HCV infection and advanced NAFLD in a large, well-characterized cohort of asymptomatic patients. Especially the high prevalence of undetected HCV infections (0.8%) emphasizes the need for HCV screening in a population-based manner. Importantly, 40% of individuals with unknown HCV infection did not show any evidence for chronic liver disease, which would leave them without diagnosis and treatment.

THU380

Does additional information obtained from multiple visits change the timing of HCV treatment decisions

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Background: PEI has a comprehensive jurisdiction-wide HCV elimination program. Past data suggests multiple visits and delayed treatment starts may be barriers to HCV care and elimination. Improved HIV health care has been demonstrated with rapid, same day treatment starts facilitated by simplified pre-treatment workup.

Aim: We evaluated the impact of standard of care workup on HCV treatment eligibility and decision making to determine the minimal data required for safe and timely HCV treatment starts.

Method: Patients were referred to the HCV program through Public Health, community providers, or “bring a friend” strategies. Four pre-visit steps were completed: 1. baseline blood work including APRI, FIB-4 and HCV viral load; 2. drug-drug interaction (DDI) checks; 3. patient-informed health-history; and 4. book a first appointment. Patient treatment eligibility and provider treatment choice was assessed at each of the four steps. Treatment naïve patients without contraindications were offered glecaprevir/pibrentasvir treatment start at the first visit.

Results: 236 patients were referred and assessed between February 2018–October 2019. 229 (97.03%) were considered treatment eligible before step 1–4 workup (6 adolescents excluded). All 197 individuals

with APRI <1.5, and detectable HCV viral load were deemed eligible for HCV treatment on the first visit and moved to step 2. 23/197 (12%) patients had a step 2 DDI screen identifying them as needing co-medication (statin, ethyl-estradiol, high dose quetiapine) adjustment before treatment start in step 2. All step 2 patients had a health history completed in step 3, and no treatment decisions were altered based on the health history. Of the 224 (94.92%) people dispensed medication at step 4 first visit, 100 (44.64%) achieved SVR12, 90 (40.18%) are pending SVR12, 26 (11.61%) are currently on treatment. In total, 5 (2.23%) treatment failures occurred and no individuals have been lost to follow-up. No serious adverse events or liver related decompensation occurred. failures occurred. No significant safety issues were noted.

Conclusions: APRI, HCV viral load, and DDI are key to deciding rapid treatment starts, and further information did not alter treatment timing or choice. Rapid treatment starts are safe and effective in the vast majority of HCV referrals, and facilitated high follow-up and cure even in difficult to engage populations. A streamlined, rapid treatment start approach may be an effective HCV elimination tool as part of a comprehensive program.

THU381

Missed linkage to care for patients with chronic hepatitis C virus infection in a tertiary care center: results of the telepass project

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Background and Aims: Italy is one of the twelve countries worldwide considered on track to eliminate hepatitis C virus (HCV) by 2030. To achieve this goal, continuous effort is required in designing efficient case finding and linkage to care strategies. In this scenario, health-care facilities are crucial to seek infected patients who have not yet been treated, but the absence of specific management policies can hinder their linkage to care. We investigated the prevalence of HCV infection in a large cohort of patients and the effectiveness of a recall strategy for patients diagnosed with chronic HCV infection in a tertiary care center but not linked to care.

Method: The Telepass project, called "Telepass" from the name of the preferential lanes on the highway, was structured in: 1) a retrospective phase, aimed at identifying all anti-HCV positive subjects among patients who underwent pre-operative assessment between March 2017 and March 2018 in a tertiary care center in Central Italy (case finding) and 2) a prospective phase, finalized to the recall of all patients requiring further diagnostic tests (i.e. HCV-RNA) or treatment (linkage to care).

Results: A total number of 12246 records of patients tested for anti-HCV antibodies was reviewed. The overall prevalence of anti-HCV positive subjects was 1.83% (224/12246), which was significantly higher in men than in women (110/3890, 2.82% vs. 114/8356, 1.36%; p < 0.00001). No patient under the age of 25 was found anti-HCV positive and the prevalence increased from 0.85% in subjects aged 25 to 49 to 4.73% in those over 80. No information on the HCV-RNA test was available for 123 (54.91%) of these anti-HCV positive patients. Twenty-six out of them (21.13%) were referred for hepatological evaluation, 10 (38.46%) resulted HCV-RNA positive and started treatment with direct-acting antivirals (DAAs).

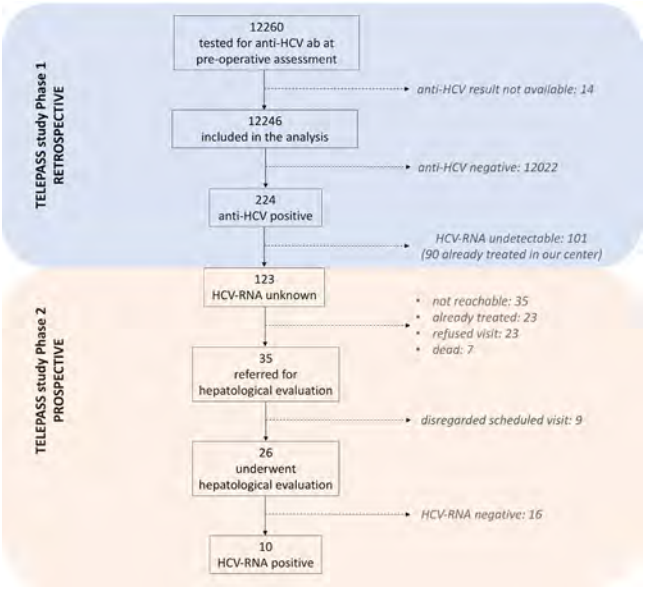

Figure: Flow diagram of patients' recruitment in the Telepass study.

Conclusion: The Telepass study highlights that a recall strategy starting from internal hospital databases is mandatory to link to care hidden patients with chronic HCV infection. Furthermore our study provides an epidemiological insight on the prevalence of HCV infection in Italy in the late DAAs era in order to plan targeted campaigns for screening and to program economic resources for treatment.

THU382

Epidermal growth factor gene polymorphism in hepatitis C virus patients with hepatocellular carcinoma

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Background and Aims: Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and develops predominately in individuals with liver cirrhosis. Insights into the biology of HCC have demonstrated that accumulations of genetic abnormalities can play an essential role in liver carcinogenesis. Epidermal growth factor receptor (EGFR) is highly expressed in the liver and is upregulated in many cancers. The EGF +61A/G polymorphism (rs4444903) is a common single nucleotide polymorphism (SNP) in the 5′-untranslated region of the EGF gene, modulating the transcription of EGF gene. There is limited number of studies conducted to examine the association between EGF +61A/G polymorphism and HCC susceptibility. Our aim was to asses this association to highlight the benefit of molecular biomarkers predictive of individual HCC susceptibility, to improve guidelines for genetics-based patient screening and preventive strategies.

Method: This study included 90 subjects grouped as follows: 30 cirrhotic HCV patients with HCC, 30 cirrhotic HCV patients without HCC and 30 healthy controls. Detailed examination and routine laboratory investigations were performed. DNA extraction was done for peripheral blood samples from all cases and controls, using Qiagen DNA extraction kit. Genotyping assay was done for the EGF 61A > G polymorphisms using the fluorogenic 5′-nuclease assay according to the allele-specific primers, detecting SNP rs444903 by TaqMan Genotyping Assay Applied Biosystems ThermoFischer kit.

Results: Our study showed a statistically significant increased expression of 61*G allele of the EGF gene in the group of cirrhotic patients and group of HCC patients, in comparison to the control group, p = 0.003, p = 0.027 respectively. Genotypes AG and GG show higher incidence (36% and 33% respectively) among HCV patients with HCC.

	HCV+HCC (n = 30)		HCV (n = 30)		Control (n = 30)			
	No.	%	No.	%	No.	%	χ^2	p
Genotype								
AA	9	30.0	4	13.3	11	36.7	13.886*	0.008*
AG	10	33.3	16	53.3	18	60.0		
GG	11	36.7	10	33.3	1	3.3		
Sig.bet.Groups	$p_1 = 0.187$, $p_2 = 0.004^*$, $p_3 = 0.005^*$							
Allele								
A	28	46.7	24	40.0	40	66.7	9.249*	0.010*
G	32	53.3	36	60.0	20	33.3		
Sig.bet.Groups	$p_1 = 0.461$, $p_2 = 0.027^*$, $p_3 = 0.003^*$							

Figure: Comparison between the three studied groups according to genotype
p_1: p value for comparing between the **HCV+HCC** group and **HCV** group.
p_2: p value for comparing between the **HCV+HCC** group and **Control** group.
p_3: p value for comparing between the **HCV** group and **Control** group.

Conclusion: The HCC surveillance programs that could lead to early cancer detection and effective treatment are based on heterogeneous scoring systems that require costly measures. Our study revealed that it is of clinical benefit to identify genetic traits as EGF +61 A/G polymorphism, that can modify liver carcinogenesis, and potentially be used to improve preventive and therapeutic strategies in HCC management.

THU383

Impact of dysmetabolism on liver damage severity and evolution in a real-life cohort of patients treated for chronic hepatitis C

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Background and Aims: Aim of this study was to examine the impact of dysmetabolism on liver disease in a real-life region-based registry of patients, who recently underwent therapy for chronic hepatitis C virus (HCV) infection with direct antiviral agents (DAAs).
Method: From the NAVIGATORE-Lombardia Network database, we extracted the records of 7,009 patients, for whom age, sex, body mass index, baseline severity of liver fibrosis (by liver histology and/or Fibroscan), diagnosis of treated diabetes, hypertension and hyperlipidemia were available. In 748 patients, liver stiffness measurement by Fibroscan at 24 weeks after the end of therapy was available.
Results: Mean age was 61.3 ± 12.7 years, 42.4% were females, 14.8% HIV+, 50.0% had cirrhosis. 8.3% were underweight (BMI < 25), 49.3% had normal weight (BMI 20–25), 31.7% were overweight (BMI 25–30), and 10.7% obese (BMI > 30); 33.3% had hypertension, 10.3% diabetes, and 4.3% treated dyslipidemia.
Higher BMI and type 2 diabetes were independently associated with fibrosis stage and baseline LSM (p < 0.0001 for all). The association remained significant after excluding cirrhotics. Diabetes and hypertension were associated with higher FIB-4 (p < 0.001). Those treated for dyslipidemia had less severe liver damage (p < 0.001). Severe fibrosis was independently associated with older age, male sex, HIV coinfection, HCV genotype, BMI and the presence of diabetes. The impact of higher BMI was larger in those without than in those with diabetes (p = .003).
Sustained virologic response (SVR) was achieved by 97.7% participants. SVR was negatively impacted by male sex, cirrhosis, and infection by genotype 3-HCV, but not metabolic cofactors. Among those who did not achieve SVR, diabetes and obesity were associated with FIB-4 worsening at 12 weeks after the end of therapy.
In the subset of patients for whom follow-up LSM evaluation was available, at multivariate generalized linear model LSM improvement was independently associated with higher baseline levels (p < 0.001), SVR achievement (p = .025), and absence of diabetes (p = .001).
Conclusion: We detected a high rate of metabolic comorbidities, except for dyslipidemia, in particular in subjects with severe fibrosis. We confirmed a strong association of diabetes and adiposity with liver damage severity. Diabetic patients remain at high risk of progression after HCV eradication. We are currently evaluating the impact of dysmetabolism and fatty liver on clinical events during follow-up.

THU384

Direct-acting antivirals have substantially modified the profile of patients with cirrhosis who require hospitalization in Spain

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Background and Aims: In 2015 the Spanish government set a goal of eliminating hepatitis C. Since then, more than 130.000 patients have been treated with direct-acting antivirals (DAAs). Our aim was to evaluate the impact of DAAs on the profile of patients with liver cirrhosis (LC) admitted to a liver unit of a referral hospital.
Method: Review of electronic health records of all patients admitted to a referral Liver Unit from 2011 to 2019. Patients hospitalized due to acute hepatitis, liver transplantation or a diagnosis different from LC were excluded. Demographic variables, causes of admission, days of admission, intensive care requirement, and clinical outcomes (discharge, death) were recorded. The aetiology of LC was reviewed individually and validated by a physician.
Results: Data for 2011, 2014, 2017 and 2018 have been obtained so far. 6449 admissions (corresponding to a total of 3742 patients) have been analysed. After applying the exclusion criteria, 4354 admissions corresponding to 2451 patients with LC, were included. There was a significant decrease in the number and proportion of admissions of patients with HCV-LC (2011: 47%, 2014: 53%, 2017: 36% and 2018: 30%, p < 0.01). Similarly, we found a significant decrease in the number and proportion of patients admitted for HCV-LC (2011: 50%, 2014: 48%, 2017: 35% and 2018: 32%, p < 0.01). Excluding patients with hepatocellular carcinoma, admissions due to HCV-LC dropped from 36% in 2011 to 19% in 2018, and the number of admissions due to acute decompensation in HCV-LC declined a 50% within the same period. Regarding HCV infection markers, the proportion of HCV-LC patients with positive HCV-RNA decreased from 94% in 2011 to 35% in 2018, p <0.01. Overall, the proportion of total days of admission per year due to HCV-LC dropped significantly (2011:44%, 2014: 50%, 2017: 33% and 2018: 25%, p < 0.01) as well as the number of episodes requiring intensive care support (from 46% in 2011 to 24% in 2018, p < 0.01). Most importantly, hospital mortality due to HCV-LC decreased from 51% in 2011 to 24% in 2018, p < 0.01). Interestingly, hospitalization episodes due to LC caused by NASH increased significantly (from 1.7% in 2011 to 10.2% in 2018), as well as those due to autoimmune LC (1.2% in 2011 to 4.4% in 2018).
Conclusion: The efficacy of interferon-free therapy has modified the profile of patients with LC undergoing hospitalization, by reducing the weight of HCV-LC. Moreover, during the last few years there has

Baseline Characteristics					
	Control Group n=359	Telephone Group n=367		Incentive Group n=333	
			p		p
Mean Age (±SD)	47.4 (9.4)	48.2 (8.9)	0.68	48.0 (8.9)	0.70
Male (%)	237 (66.0)	225 (61.3)	0.19	219 (65.8)	1.00
History of IVDU	210 (58.5)	217 (59.1)	0.88	207 (62.2)	0.35
History of >50u alcohol / week	66 (18.4)	77 (21.0)	0.40	76 (22.8)	0.19
Untreated	315 (87.7)	308 (83.9)	0.17	287 (86.2)	0.57

Figure: (abstract: THU386)

been a significant reduction in hospital morbidity and mortality attributable to patients with HCV-related LC.

THU386

Patients with hepatitis C (Redpath): a randomised controlled trial of telephone contact or offer of an incentive, in addition to a standard letter

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Background and Aims: Meeting the goals of hepatitis C (HCV) elimination requires the re-engagement of those diagnosed but no longer in clinical care. Limited evidence exists on how best to approach to such patients. We sought to establish the effectiveness of a letter combined with either a follow up phone call, or the offer of an incentive, compared to a standard letter inviting the patient to re-engage.

Method: Patients on the Greater Glasgow & Clyde (NHS GG&C) copy of the Scottish HCV database, with a community health index (CHI) number were identified. Those untreated, treated unsuccessfully, or with unknown outcome were selected. Cross checking with the CHI database identified and excluded patients who were deceased or no longer resident in GG&C. Patients were randomised to receive one of three letters. Group A (control): a letter outlining the consequences of untreated hepatitis C, the availability, tolerability and efficacy of new treatments, and a contact number to arrange an appointment. Group B (phone): additional text indicating an attempt to contact the patient by phone would be made if no response within 4 weeks, Group C (incentive): additional text offering a £20 (~€23) shopping voucher if contact made within 4 weeks. For Group B, 2 attempts to contact the patient by phone were made if they had not made contact by week 4, with a standard message left if voicemail in use. The primary outcome measure was attendance at hospital or outreach clinic for assessment of liver disease within 4 months of the letter. The secondary outcome was commencement of treatment within 6 months. We present an interim analysis of attendance at 3 months. Categorical variables were analysed using Fisher's exact test, continuous variable using student's t-test, comparing each intervention arm to the control.

Results: 1059 patients met the inclusion/exclusion criteria. The majority of patients were male, with a history of intravenous drug use, and were naïve to treatment (table 1). No significant differences in baseline characteristics were seen between groups. At 3 months 135 (12.7%) of patients had attended for assessment, 38 (10.6%) control, 57 (15.5%, p = 0.048) phone, 73 (12.0%, p = 0.55) incentive.

Conclusion: Interim results suggest that a letter with follow up phone call is more likely to reengage patients lost to follow up with HCV than a letter alone, or a letter plus offer of incentive. Full results on attendance and initiation of treatment according to intervention group will be presented.

THU387

Overdose events among active drug users successfully treated for HCV: the impact of homelessness

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Background and Aims: Since 2015, the opioid crisis has led to over 5,000 overdose deaths in British Columbia, Canada. Previous studies have demonstrated increases in risky drug use behaviour among individuals with unstable housing, a finding that may be mitigated by engagement in care, which may occur in the provision of HCV treatment to this priority population. We sought to evaluate the interaction of homeless and overdose events in a group of drug users having received HCV therapy in the context of a multidisciplinary system of care.

Method: We conducted a retrospective analysis of active drug users engaged in HCV treatment at our centre from 01/15–10/19, as a function of their housing status. All patients were enrolled in multidisciplinary care addressing their medical, social, psychological, and addiction needs. The primary endpoints of this analysis are correlates and occurrence of medically significant overdose events, including mortality.

Results: We compared 211 (74%) well-housed and 75 (26%) homeless active drug users engaged in HCV care at our centre. Of these, 25 remain on HCV therapy and 243/261 (93%) others achieved a cure of their infection and remain in care. Mean age among well-housed active drug users was 53 years, 25% female, 55%/30%/39% opioid/amphetamine/cocaine use, 53% on opioid substitution therapy (OST), 50% psychiatric comorbidities. Among homeless active drug users, mean age was 52 years, 13% female, 76%/48%/45% opioid/amphetamine/ cocaine use, 56% on OST, 64% psychiatric comorbidities. Among well-housed active drug users, 18 individuals experienced medically significant overdose events and there were 7 deaths (12% event rate). Among homeless active drug users, 13 individuals experienced medically significant overdose events and there were 3 deaths (21% event rate).

Conclusion: Among HCV-infected active drug users engaging in care at our centre, one quarter were homeless, who were more often male, more active poly-substance users and with a higher prevalence of psychiatric co-morbidities. Overdose events (including mortality) were twice as frequent in this population. Although engagement in care served to reduce the occurrence of opioid-related events by over 50% compared to the overall population of active drug users in the community, homelessness remains associated with a higher risk of events even in the setting of provision of HCV care in a multidisciplinary setting. This setting will provide the ideal setting to evaluate additional interventions to reduce opioid-related events, particularly in the homeless population.

THU388

Micro-elimination in prisons: a high-intensity test and treat (HITT) programme

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Background and Aims: If countries are to meet the WHO target of elimination of HCV, all patients at risk of HCV must be identified and treated. Prisons are a high prevalence site with high throughput of people who in inject drugs. A High Intensity Test and Treat (HITT) initiative is one potential approach to try and micro-eliminate HCV in prisons. Leeds is a medium secure local prison and was chosen as a site to trial this approach. The aim was to test and treat as many prisoners as possible over a two weeks period.
Method: Prior to testing commencing a publicity campaign was conducted by peers within the prison and prisoners were incentivized to be tested by providing chocolate bars and telephone access cards. Over the course of a weekend period in July 2019 an attempt was made to test all inmates in the prison for HCV, Hepatitis B (HBV) and Human Immunodeficiency Virus (HIV) with a point of care Matrix test. Positive antibody tests were further tested with capillary blood PCR tests performed in the local laboratory with test result turnaround of 24 hours. Prisoners testing PCR positive were immediately informed of the diagnosis and a review of their current drug history made to check for drug drug interactions. If a genotype was already available on their medical record they were treated with an appropriate genotype specific drug or if no genotype was available they were treated with the pan-genotypic drug Maviret.
Results: There were 1022 in Leeds prison during the course of the testing weekend. 757 prisoners were tested but 47 refused to be tested and 218 could not be accessed within the prison to be tested. Only 1 prisoner with HIV and 1 prisoner with HBV were identified and these were already known to treatment services. 59 of 757 tested prisoners were HCV antibody positive (7.8%) and 36/757 (4.8%) were PCR positive. 9/36 were already on or about to start treatment and 8/36 were released or transferred to another prison in the week between testing and commencing treatment. One prisoner died during this period. 15 new patients started treatment during the course of the two weeks project. Treatment completion and sustained virological response rates are awaited.

Outcome	No	Outcome	No
Started treatment	15	Started treatment prior to HITT	7
Retreatment	3	Pending treatment	2
Transferred	1	Released lost to follow up	7
Deceased	1	Total	36

Figure: Treatment Starts for HCV RNA Positive Prisoners.

Conclusion: HITT is an effective approach to micro-eliminate HCV in prisons. Not all prisoners identified by this program are new diagnoses. Due to the high throughput of prisoners it is essential that treatment is commenced immediately after diagnosis or prisoners may be lost to follow up.

THU389

Oncogenic implications of sofosbuvir on the development of hepatocellular carcinoma

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Background and Aims: Hepatitis C virus (HCV) is a major cause of liver cirrhosis and hepatocellular carcinoma (HCC) in Taiwan. Direct-acting antivirals (DAAs) have achieved a sustained virological response (SVR) rate around 95–98% in treating HCV. Several studies suggested that treatment with DAAs may be associated with increased risk of developing HCC in the first 6–12 months. The aim of the study is to investigate the oncogenic implication of sofosbuvir (SOF) on the development of HCC.
Method: OR-6 (harboring full length genotype 1b HCV) and Huh 7.5.1 cells were used in the study. We'll examine the effects of SOF on cell proliferation, migration and invasion assay in hepatoma cells. We also will inspect the potential molecules involved in tumorigenesis effects of SOF in OR-6 cells treated with SOF using next generation sequencing (NGS). After selection of the candidate genes significantly up-regulated by SOF in OR-6 cells by NGS analysis, we'll correlate the clinical significance of these candidate genes using The Cancer Genome Atlas (TCGA) data base.
Results: We found that SOF increased cell proliferation and migration in hepatoma cells. Using NGS we have identified several genes significantly up-regulated by SOF in OR-6 cells. Among these genes, we discovered that TRIM39, TSNAX-DISC1, RPP21 and another four genes are more significantly expressed in the tumor part of HCC than non-tumor part in the TCGA data base. These genes are significantly associated with the development of HCC in the TCGA data base. Besides, siRNA mediated knock-down of TRIM39, TSNAX-DISC1 and RPP21 reduced the increased cell proliferation and migration by SOF in OR-6 and Huh 7.5.1 cells.
Conclusion: SOF up-regulated several genes associated with the development of HCC in the TCGA data base. Knock-down of these genes reduced the increased cell proliferation and migration by SOF in hepatoma cells.

THU390

Epidemiological evolution of viral hepatitis in uremic patients in Taiwan - the Formosa like group

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Background and Aims: Hepatitis B virus (HBV) and hepatitis C virus (HCV) are leading causes of chronic liver disease in hemodialysis patients in Taiwan. The treatment of HCV may be underappreciated even in the era of directly acting antivirals. Evolution of the seroprevalence of viral hepatitis and HCV treatment rate in this special population is elusive. We aimed to address the issue by performing consecutive surveillances upon the population.
Method: The Formosan Coalition for the study of Liver Disease in Chronic Kidney Disease (FORMOSA-LIKE group) consisted of 18 hemodialysis centers in 2012 and expanding to 22 centers in 2019. A total of 490 uremic patients participated both of the first mass screen in 2012 and second mass screen in 2019. All subjects were tested for HBV and HCV serology and virology.
Results: The seropositive rates of anti-HCV, HBsAg and both HBsAg/anti-HCV were 15.7% (n = 77), 14.3% (n = 70) and 2.5% (n = 12), respectively, in 2012, and 16.3% (n = 80), 13.3% (n = 65), and 3.1% (n = 15), respectively, in 2019. The HCV viremic rate among anti-HCV seropositive patients decreased significantly from 71.4% (55/77) in 2012 to 52.5% (42/80) in 2019 (p = 0.015). Thirty-nine of the 55 HCV viremic patients in 2012 had persistent viremia in 2019, whereas 16 patients became HCV RNA undetectable. Of them, 12 patients were due to HCV eradication by antivirals ([interferon [IFN]-based (n = 1), IFN free-directly acting antivirals (n = 11)] and the other 4 experienced spontaneous HCV clearances. Seven patients got new HCV

infection, including one anti-HCV seropositive patient without viremia in 2012 became viremic in 2019, and 6 anti-HCV seronegative patients became anti-HCV seropositive in 2019 (five had viremia and one was with spontaneous HCV clearance). The annual incidence of new HCV infection was 0.24% (7/490). The HCV treatment rate was 5.2% (3/58) and 21.1% (12/57) in 2012 and 2019, respectively (p = 0.01). Two patients had new HBsAg seropositivity (0.07%/year) and 7 HBsAg antigemic patients experienced HBsAg loss (0.23%/year).
Conclusion: Viral hepatitis prevails with new infection occurrence in uremic patients. The treatment of HCV infection is underutilized. Link-to-care and outreach onsite treatment are mandatory to increase the treatment uptake of HCV in the highly contagious population.

THU391

Safety and efficacy of an all-oral interferon-free regimen of seraprevir, an NS3/4A protease inhibitor and sofosbuvir in patients with chronic hepatitis C virus (HCV) genotype 1: an open-label,multicentre, phase 3 trial

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Background and Aims: This phase 3, single-arm, open-label, multi-center study was conducted to evaluate the safety and efficacy of an all-oral interferon-free regimen of **Seraprevir**, an NS3/4A protease inhibitor and sofosbuvir for 12weeks in patients with chronic hepatitis C virus (HCV) genotype 1.

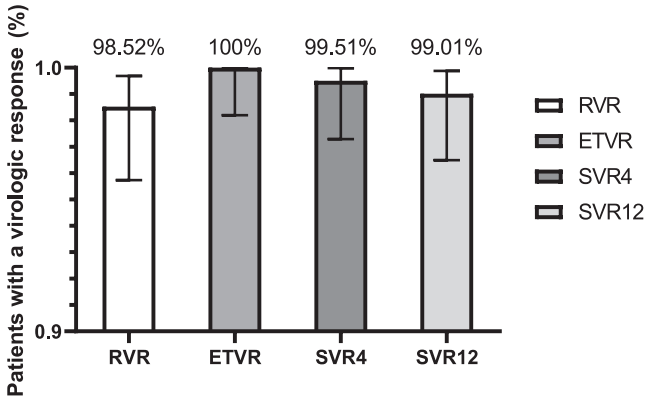

Figure 1. Efficacy of Seraprevir and sofosbuvir in patients with HCV genotype 1 infection.

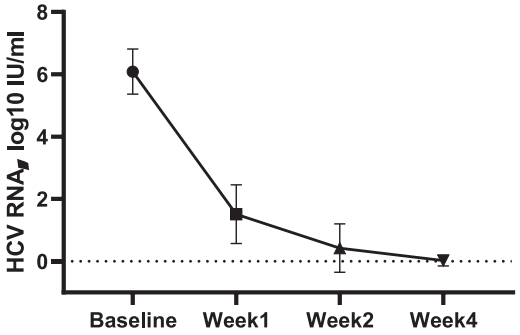

Figure 2. Changes in viral load from baseline to week 4.

Method: In this multicenter ongoing trial, 205 patients wererecruited from 23 sites in China. Eligible participants were aged 18–75 years with non-cirrhotic, chronic HCV genotype 1 infection and were 86.8% HCV treatment-naïve (178/205) or 13.2% treatment-experienced (27/205). Patients received once-daily sofosbuvir (400 mg) plus twice-daily **Seraprevir** (100 mg) for 12 weeks. The primary efficacy endpoint was sustained virological response, defined as HCV RNA less than 15 IU/mL at 12 weeks after the end of treatment (SVR12), assessed in all patients who received study drug. The primary safety endpoint was the proportion of adverse events leading to premature discontinuation of study drug. This trial is registered with ClinicalTrials.gov, number 2017L00637, and is completed.
Results: Between 17. Oct. 2018, and 17. Jan. 2019, a total of 205 patients were enrolled in the study, of whom 203 completed the full treatment course and two discontinued treatment. Overall, 45.4% were male, 2.4% had GT1a, 97.6% GT 1b HCV infection. The mean (range) age of enrolled patients was 46.9y (24–73). 13.2% had ever treated by IFN. The rate of SVR12 was 99.01% in Full Analysis Set. The overall SVR4 rate was 99.51%. One subject relapsed after 4 weeks of follow-up, and 1 subject relapsed after 12 weeks of follow-up. The most common adverse events were upper respiratory tract infection (32 [15.6%] patients). There was one discontinuation due to adverse events. Serious adverse events were reported in eight (3.9%) patients, none of which was judged to be related to sofosbuvir-**Seraprevir** treatment.
Conclusion: Treatment with the single-tablet sofosbuvir-**Seraprevir** was highly effective and well tolerated in GT1 chronic HCV infected population without cirrhosis.

THU392

Expansion of a multidisciplinary support program for patients with addictions and hepatitis C: strategies for an effective approach

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Background and Aims: In June 2018 we created a multidisciplinary support program (MSP ADIC C) at the addiction center of our hospital

to improve screening, evaluation and treatment of patients with addictions and hepatitis C. The aim of the study was to expand the experience of MSP ADIC C to the entire reference area of our hospital.
Method: we created a collaborative network of addiction centers from our reference area since February 2019. The MSP expansion has been based on: a) Screening of HCV infection at every addiction center and a fast-track referral to our MSP located in the hospital premises; b) Implementation of social educators who accompanies patients to the scheduled visits; c) Simplification of the evaluation and treatment process ("all-in-one" visit); d) Outsourcing Hospital Pharmacy; e) Coordination and evaluation. Variables related to sociodemographic and clinical aspects have been collected prospectively. We defined the impact of the MSP expansion as the increase of patients included monthly. Antiviral regimen depended on the potential drug-to-drug interactions. Treatment adherence has been analyzed in patients who have completed antiviral therapy. Follow up visits have been scheduled after achieving sustained virological response (SVR) in order to detect reinfection.
Results: We have included 56 patients from 5 addiction centers from February 2019. The expansion of the MSP has increased the number of new patients from 1,5 to 4 new patients/month (60%). The majority were men (37/56, 66%) with a median (range) age of 46 years (25–66) and 23/56 (41%) coinfected with HIV. Twenty-three out of 56 (41%) had been referred to the Hepatologist in the past but never attended the scheduled appointments. Twenty-one out of 56 (37.5%) had no stable housing. Thirty-five out of 56 (62.5%) presented recent/active drug consumption and 51/56 (91%) were under opioid substitution therapy. Thirteen patients (23.2%) were naive and 13/56 (23.2%) presented advanced fibrosis. So far, 42 patients have completed treatment with a median (range) adherence of 98% (85–100). Nineteen out of 20 (95%) patients have achieved the SVR. Nine patients (16%) were lost during follow up. To date we have not detected any reinfection
Conclusion: The expansion of the MSP ADIC C has increased significantly the number of patients with addictions that benefits from the Program and has proved to be an effective approach for achieving HCV elimination in our reference area.

THU393

Improvement of all HCV care cascade steps in IVDU treated with DAAs within a dedicated program

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Background and Aims: Screening, linkage to care and HCV treatment of past and recent intravenous drug users (IVDU) remain one of the most challenging topics in HCV eradication. In Italy, outpatients services for substance use disorders (SERDS) disseminated on the region's territory are not allowed to prescribe direct acting antivirals (DAAs). Puglia is a Southern Italian region 400 km long, and public transportation represents an additional barrier to treatment for IVDU needing to reach prescribing centres. The estimated number of IVDU in our region is 4500, the screening rate is lower than 50%. During 2018, a total of 218 IVDU have been linked to care and treated at our centre.
To improve HCV care cascade we designed a dedicated one-year program starting on June 30th, 2019 for IVDU in our geographical area, including "ad hoc" transportation.
Method: In this prospective study, 15 SERDS are connected with our Unit. The service at our Unit offers a daily fast track program of diagnosis and linkage to care to patients screened by OraQuick HCV (OraSureTechnologies Inc) at their SERDS. Patients evaluated at baseline at our centre were treated with DAAs as per physician clinical judgement. The study completed the first three months of enrollment.
Results: Of 450 patients screened at 15 SERDS, 219 HCVAb+ve were identified. Of them 109 resulted HCV RNA+ve and 109 were linked to care as compared to 73 during the previous year. Baseline characteristics of patients included in the Table. Of treated patients 89 (82%) completed treatment and follow-up wk4. Overall, SVR4 was 99% without difference between active or past IVDU. No significant DDI limited treatment. According to these preliminary results an increase of about 70% in the number of treatments was registered.

	HCV RNA+ve N=109	HCV RNA-ve N=110	HCV Ab+ve N=219
Median age (yrs) range	47.9 (22-71)	49.5 (29-69)	48.5 (22-71)
Male gender n,%	96 (88)	90 (81)	186 (85)
Mean BMI (range)	26.7 (18-49)	27.0 (18-40)	26.8 (17-49)
Diabetes n, (%)	16 (15)	6 (5)	22 (10)
Mean HCV RNA IU/ml range	2.060.000 (39-10^7)	na	2.060.000 (39-10^7)
Genotype n, (%) 1 2 3 4 Mixed Not detected	 52 (48) 4 (3.9) 45 (41) 7 (7) 1 (0.1)	110 (100)	na
PLT <100.000/mm^3 n, (%)	7 (6)	2 (2)	9 (4)
Liver stifness >12.5 Kpa n, (%)	38 (35)	10 (9)	48 (22)

Figure: (abstract: **THU393**): Baseline characteristics of HCVAb+ve patients

Conclusion: Treatment programs based on "ad hoc" services for IVDU are associated with significant improvement in all HCV care cascade steps. Despite substance use, a single patient was lost to follow-up.
Funding: This work was supported by Gilead for the study "The Puglia microelimination" NCT03923595.

THU394

Real-life efficacy and safety of direct-acting antivirals in patients with liver cirrhosis and history of hepatic decompensation: EpiTer-2 study

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Real-life efficacy and safety of direct-acting antivirals in patients with liver cirrhosis and history of hepatic decompensation: EPI-TER2 Study

Background and Aims: The aim of this study was to assess the real-life efficacy and safety of DAAs in patients with cirrhosis and history of hepatic decompensation compared to those with compensated cirrhosis, and to identify predictors of adverse events during treatment.

Method: Data of patients with chronic hepatitis C treated in Poland with DAAs and included in the EpiTer-2 database (N = 10,152) were collected retrospectively. A total of 316 patients with decompensated cirrhosis and 2397 patients with compensated cirrhosis were selected. The efficacy endpoint was sustained viral response (SVR) at 12 weeks posttreatment.

Results: The overall SVR rate was 91.4% in the intent to treat (ITT) analysis and 95.2% in the modified ITT (mITT) analysis ($p < 0.001$). Patients with decompensated liver disease had lower SVR rates in ITT analysis (86.4% vs 92.0%, $p < 0.001$) compared to those with compensated cirrhosis, while in the mITT analysis the difference was not significant (92.9% vs 95.5%, $p > 0.05$). Genotype 3 (OR 7.7; 95% CI 2.7–21.9) and BMI $\geq$ 28 kg/m^2 (OR 3.8; 95% CI: 1.4–10.4) were predictors of treatment failure. Adverse events occurred in 31.2% of patients, accounting for 144/316 (45.6%) and 702/2397 (29.3%) in patients with decompensated cirrhosis and compensated cirrhosis, respectively ($p < 0.001$). Patients with decompensated cirrhosis were at higher risk of death (5.4% vs. 0.9%; OR 6.4; 95% CI 3.4–12.3; $p < 0.0001$) or liver decompensation (21.5% vs. 1.3%; OR 25.9; 95% CI 16.8–39.8; $p < 0.0001$) during treatment/follow-up compared to those with compensated cirrhosis. Age $\geq$ 65 years (OR 2.2; 95% CI: 1.2–4.0; $p = 0.007$) and low albumins (OR 2.9; 95% CI: 1.6–5.4; $p = 0.001$) were associated with hepatic decompensation, while treatment with protease inhibitors was not (OR 0.7; 95% CI: 0.4–1.3; $p = 0.3$). Only 82.6% of patients with decompensated cirrhosis completed DAA treatment (versus 92.8% in compensated cirrhosis group; $p < 0.0001$), and were at higher risk of treatment discontinuation/modification.

Conclusion: Despite higher frequency of adverse events and treatment modifications, once completed, DAA therapy yields comparable results for decompensated and compensated cirrhosis patients.

THU395

Concomitant use of direct-acting antivirals (DDAs) and central nervous system drugs in current chronic hepatitis C patient profile

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Background and Aims: High rate of comorbidity and comedication have recently been reported in Spanish population with hepatitis C. We evaluated the potential impact of concomitant use of central nervous system (CNS) drugs and new pangenotypic DAAs (pang-DAAs).

Method: Subanalysis of an observational, multicenter and retrospective study, done during 2017, in which 3,430 Spanish patients with hepatitis C and their associated concomitant medications were identified. In this subanalysis those who were receiving as a concomitant medication one of the following therapeutic groups with action on the CNS were identified: anticonvulsants, opioid analgesics, antidepressants, anxiolytics, antipsychotics, sedatives or hypnotics. A descriptive analysis of the most common CNS drugs used in our country in this population was done. These data were crossed for drug-drug interactions (DDIs) by the tool of the University of Liverpool with the pang-DAAs available in Spain (GLE/PIB, SOF/VEL and SOF/VEL/VOX).

Results: We identified 1,170 patients (34%) with hepatitis C who were receiving concomitant medication with CNS action (ATC N group): 744 (28%) patients with psycholeptic-anxiolytics, 679 (20%) with psychoanaleptics-antidepressants, 494 (14%) antiepileptics and 429 (13%) analgesics. Among the active principles belonging to these therapeutic groups and that showed potential DDIs with a panG DAAs included (>10 patients): quetiapine (n = 117), fentanyl (79), paliperidone (79), buprenorphine (51), oxycodone (38), aripiprazole (33), oxcarbamazepine (32) and clotiapine (19). The magnitude of the DDIs is labelled in Liverpool as contraindicated medication/red (oxcarbazepine), weak Interaction/yellow (buprenorphine and clotiapine) and significant Interaction/orange (the rest). With GLE/PIB seven of the eight CNS drugs showed potential DDIs (1 contraindication and 6 significant Interaction), three with SOF/VEL/VOX (1 contraindication, 1 significant Interaction and 1 weak Interaction), and two with SOF/VEL (1 contraindication and 1 weak Interaction) [see figure].

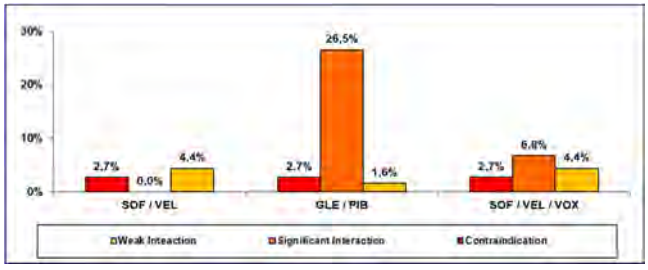

Figure: Potential DDIs between PanG-DAAs and CNS drugs (n = 1,170).

Conclusion: This analysis shows that one in three patients with hepatitis C has concomitant use of CNS drugs. Selection of a pang-DAAs with no interactions with this class of drugs is important to simplify HCV treatment. The presence of protease inhibitors in pang-DAAs may increase the number of CNSs DDIs. SOF/VEL has a lower level of interactions than other pang-DAAs.

THU396

Glecaprevir/pibrentasvir for the treatment of hepatitis C virus infection among active drug users: the grand plan study

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Background and Aims: In order to achieve the WHO objective to eliminate HCV infection as a public health concern by 2030, specific strategies to identify active drug users who are infected and to engage them in care will be required. The availability of shorter course treatment regimens may allow for more efficient use of available resources and better adherence to the entire course of medications. We describe a program for the identification of vulnerable inner-city residents living with HCV infection and their engagement in a multidisciplinary program for the administration of antiviral therapy with glecaprevir/pibrentasvir (G/P).
Method: Using a community-based recruitment program (weekly outreach clinics on the Downtown Eastside of Vancouver), we identified individuals with a prior diagnosis of chronic HCV who were disengaged from care. Other individuals presented to our center by self-referral, referral from a corrections facility, or direct recruitment by existing participants in our program. All subjects were offered a broad-based intervention to address medical, social, psychiatric and addiction-related needs. Cirrhotic patients were excluded. HCV therapy was delivered in this context, with G/P dispensed on a daily, weekly or monthly basis (8 week course of treatment) to support adherence as required. The endpoint of this analysis is the achievement of a cure of HCV infection, defined as an undetectable HCV RNA 12 or more weeks after the end of treatment (SVR12).
Results: To date, 50 patients have been enrolled (mean age 47 years, 80% male, 50%/30%/46% fentanyl/cocaine/amphetamine use and 40% with an active psychiatric comorbidity, with 64% on opioid agonist therapy and 62% unstably housed at treatment start). Twenty-five patients have completed therapy, with no premature treatment discontinuations. Post-treatment, all patients (25/25) remain in follow-up, with 6 having reached the SVR12 time point and all 6 achieving SVR (SVR12 rate 100% for eligible patients). There have been no deaths in this population at high risk of opioid overdose. Treatment outcome in all patients will be available by March 2020.
Conclusion: When delivered within the context of a multidisciplinary program of care, HCV therapy with G/P for 8 weeks is highly effective in a vulnerable and marginalized population with a high prevalence of HCV infection. Approaches such as this will be an important part of HCV elimination over the next decade.

THU397

Direct-acting antiviral treatment in patients infected with a non-epidemic hepatitis C genotype in the Netherlands: results from a nationwide cohort study

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Background and Aims: The majority of HCV infections are found in low- and middle-income countries (LMIC), with many region-specific endemic HCV subtypes. Nevertheless, trials with current direct-acting antivirals (DAA) were almost exclusively executed in high-income countries, where mainly global epidemically spread HCV subtypes are present. Recently, both clinical trials from LMIC and real-world studies from the Western world showed a sub-optimal DAA efficacy in certain HCV subtypes, which could hamper the global elimination of HCV. Therefore, the aim of this study was to investigate real-world efficacy of DAA treatment in all patients with a non-epidemic HCV genotype treated in the Netherlands.
Method: We performed a nationwide retrospective cohort study. All Dutch laboratories performing HCV genotyping participated. Patients infected with a non-epidemic HCV genotype and treated with an interferon-free DAA regimen were included. Non-epidemic HCV genotypes were defined as genotypes other than 1a, 1b, 2a, 2b, 3a, 4a or 4d. Genotype was determined by phylogenetic analysis of a 386 bp fragment of the NS5B region. Primary endpoint was SVR-12.
Results: We identified 122 patients. Most patients originated from either Northern Africa (31, 25%), South America (28, 23%), Sub-Saharan Africa (21, 17%) or South-East Asia (19, 16%). Cirrhosis was reported in 27 (22%) patients. SVR-12 data was available for 111 (91%) patients, of whom 100 (90%) reached SVR-12. Genotypes and SVR-percentage per genotype is shown in table 1. Remarkably, only 65% of patients with genotype 3 infection reached SVR-12, due to three failures in genotype 3b infections.

Genotype (n, %)	Subtypes (n)	SVR-12 (%, n/n)
1 (14, 13%)	c(6), d(1), g(7)	93% (13/14)
2 (44, 40%)	c(3), d(1), e(2), f(2), i(6), k(1), unassigned(29)	91% (40/44)
3 (8, 7.2%)	b(6), k(2)	63% (5/8)
4 (35, 32%)	c(2), f(2), h(5), k(4), l(2), n(6), o(6), q(1), r(3), t(1), v(1), unassigned(3)	94% (33/35)
5 (1, 0.9%)	a(1)	100% (1/1)
6 (9, 8.2%)	a(4), e(1), unassigned(4)	89% (8/9)

Figure: (abstract: THU397): non-epidemic HCV genotypes with SVR-12 result

Conclusion: DAA treatment results in most non-epidemic genotypes in the Netherlands seem reassuring. However, the low SVR-12 rate in genotype 3 infections is alarming, especially as this genotype is common in certain countries with high HCV prevalence. Together with earlier published results, these results show that one of the remaining challenges for global HCV elimination is confirmation and monitoring of DAA treatment effectiveness in non-epidemic genotypes.

THU398

A real-world study of treating advanced liver cirrhosis due to chronic HCV infection genotype 1b with sofosbuvir+ ledipasvir with or without ribavirin: results from a cohort of 349 patients

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Background and Aims: Sofosbuvir+Ledipasvir±Ribavirin showed good results in terms of efficacy and safety in clinical trials in advanced liver cirrhosis, but real life data are still needed in order to confirm this profile.
Method: We analyzed a multicentric prospective cohort enrolling 349 patients with liver cirrhosis (210 decompensated, 139 compensated) due to chronic hepatitis C who received Sofosbuvir + Ledipasvir ± Ribavirin for 12/24 weeks (301/48). Patients were included between september 2018- september 2019 and all of them had genotype 1b. Main inclusion criteria were liver cirrhosis and detectable HCV RNA. The cases were followed-up monthly during therapy and then at 12 weeks after the end of therapy.

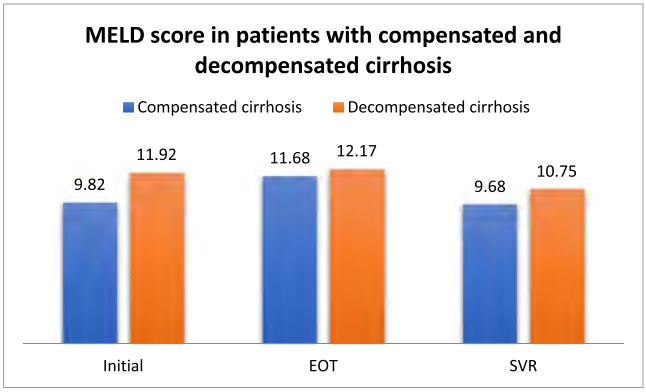

Figure: The evolution of MELD score in patients with compensated and decompensated cirrhosis and HCV infection treated with Sofosbuvir + Ledipasvir ± Ribavirin.

Results: 6 patients were lost during follow-up and in 16 patients (4.6%) treatment was interrupted due to adverse events: 9 with worsening hepatic decompensation (4.3%), 4 patients had cardiovascular events, 1 severe alergy and 2 bacterial infections. This cohort had 60% females with a median age of 61 years (37÷83), 12.4% IFN pre-treated, 50% with co-morbidities, 7% with Child Pugh C, 5% with virus B co-infection and 7% with treated HCC. Mean initial MELD score was 10.92 ± 3.01 (7.1÷24.5). Sustained viral response in intention to treat was reported in 175/210 (83.3%) in patients with decompensated cirrhosis and 122/139 (87.8%) in cases with compensated cirrhosis. The evolution of MELD score is depicted in figure. Predictive factors of SVR in decompensated cirrhosis were: decreased bilirubin ($p = 0.01$), absence of ascites ($p = 0.008$) and lower Child Pugh score ($p = 0.01$). In compensated cirrhosis female sex ($p < 0.001$), advanced age ($p = 0.001$), absence of ascites at therapy initiation ($p = 0.018$), no history of variceal bleeding ($p = 0.05$) predicted SVR.
Conclusion: Sofosbuvir+Ledipasvir±Ribavirin proved to be highly efficient in our difficult to treat population with 83.3% SVR in decompensated cirrhosis and 87.8% in compensated cirrhosis. Serious adverse events were reported in 16/349 (4.6%), most of them due to severe liver decompensation (9/16). Predictors of SVR in decompensated cirrhosis were: decreased bilirubin, absence of ascites, low Child Pugh score, while in compensated cirrhosis female sex, advanced age, absence of ascites and no history of variceal bleeding predicted a good response.

THU399

Alcohol use does not influence treatment uptake or outcomes in the DAA era

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Background and Aims: Alcohol use is well recognized for accelerating liver disease in the context of HCV and often led to delayed initiation of interferon-based treatment. To successfully eliminate HCV, it is important to treat all persons living with HCV, including those in difficult to treat individuals. However, there are limited data on the influence of alcohol use on treatment initiation and outcome in the DAA era.
Method: The Canadian Network Undertaking against Hepatitis C (CANUHC) Cohort contains prospectively collected demographic information and HCV DAA treatment information collected at 10 Canadian sites. Self-reported alcohol (define as: (a) any use, (b) number of drinks per day/week/month) and other recreational substance use is collected. Characteristics and outcomes (SVR) were compared by past and present alcohol use.
Results: Since January 2016, 725 HCV-infected patients under assessment for DAA therapy were enrolled in CANUHC (mean age: 53 (SD 12.7); 66% male; 78% White, 5% Indigenous, 4% South East Asian, 4% South Asian, 3% Black). Any past and present alcohol use was reported by 37% and 30%, respectively. Mean age was older in those with [54.5 (SD 11.9)] vs without current alcohol use [51.9 (SD 12.9), $p < 0.01$]. A similar proportion of males (31%) and females (27%) reported current alcohol use ($p = 0.27$). The overall mean (10.8 kPa (SD 10.0) vs 10.9 kPa (SD 9.2)] and median (F2) baseline fibrosis measures were similar in current alcohol users. Treatment initiation during the period of evaluation was similar in current alcohol (42%) vs non users (39% in both groups, $p = 0.52$). SVR rates of 92.3% and 92.0% were similar in those with and without current alcohol use ($p = 0.93$).
Conclusion: DAA antiviral therapy is successful irrespective of past or current self-reported alcohol use. There is no evidence of diminished SVR in those concurrently using alcohol. These findings provide support from the Canadian context to recommend treatment of all people living with HCV, particularly in the context of alcohol use, in HCV elimination efforts.

THU400

Influence of baseline resistance on treatment outcome in patients treated for chronic hepatitis C in Denmark: a nationwide study

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Background and Aims: Direct acting antivirals (DAAs) have proven highly effective against chronic hepatitis C virus infection. However, some patients experience treatment failure, frequently associated with resistance associated substitutions (RASs). Our aim was to investigate the complete viral open reading frame (ORF) in hepatitis C patients with treatment failure, in order to detect RASs and the effects of treatment on the viral population.

Method: Chronic hepatitis C patients in the Danish Database for hepatitis B and C, who initiated DAA treatment between 1st January 2014–1st May 2015 were included and 21 patients with treatment failure were identified. We selected 22 patients with sustained virologic response (SVR) to match the 21 treatment failure patients in relation to genotype (GT), DAA regimen, liver cirrhosis and previous treatment experience. Data on viral titers were compared between the two patient groups and full-length ORF RT-PCR was performed to analyse the entire coding sequence, including identification of RASs.

Results: The proportion of NS5A RASs at baseline were significantly higher in treatment failure patients (82%) than in the matched SVR (25%) patients ($p = 0.0063$). In addition, treatment failure could be associated to slower declines in viremia titers. Viral population heterogeneity did not differ at baseline between SVR and treatment failure patients, but a bottleneck effect was observed post failure related to RASs selection. The substitution 150 V in the NS5B region at baseline was found in 4 (80%) out of 5 GT3a patients with treatment failure compared to only 1 out of 5 (20%) GT3a patients with SVR. Six retreated patients (35%) experienced 2nd treatment failure. RASs against the used DAA regimen in retreated patients were present prior to initiation of retreatment in 4 (67%) out of 6 patients compared to 2 (20%) out of 10 patients who achieved SVR after retreatment.

Conclusion: Baseline resistance to NS5A inhibitors was associated with treatment failure indicating that RAS at baseline may affect treatment outcome. The substitution 150 V in the NS5B region at baseline was associated with treatment failure to sofosbuvir in GT3a patients. The lower viral titer decline in the treatment failure group was associated with RAS present against the used DAA regimen at baseline. We found that successful DAA retreatment in patients with treatment failure was hampered by previously selected RASs. We recommend resistance testing in patients with previous DAA treatment failure before DAA retreatment in order to increase the chance of cure and prevent development of multi-resistant viruses in the future.

THU401

Inadvertent "off label" DAA treatment in the real-world and importance for virologic outcome - data from the German hepatitis C-Registry (DHC-R)

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Background and Aims: Correct selection of DAA regimens and treatment duration for patients with chronic hepatitis C depend on clinical and virologic features. Frequency and potential reduced SVR rates for off-label use are not well known.

Method: The DHC-R (German Hepatitis C-Registry) is a national multicenter real-world registry including about 16,500 patients recruited by more than 250 centers. For the present analysis, data were analyzed as of Jan 20, 2019. All patients who received Glecaprevir/Pibrentasvir (G/P), Ledipasvir/Sofosbuvir (LDV/SOF), Velpatasvir/Sofosbuvir alone (VEL/SOF), with Voxilaprevir (V/V/S) and Grazoprevir/Elbasvir (GZR/EBR) were included. Data were analyzed with respect to in-label or off-label use of the given DAA regimen according to package insert and guidelines.

Results: For pangenotypic regimens (G/P, VEL/SOF, V/V/S) off-label use was observed infrequent (4.1–5.2%) while for LDV/SOF and GZR/EBR many patients were treated outside of the label or guidelines (27.3–36.3%).

Most frequent deviations from the label for G/P and VEL/SOF were shorter or longer treatment duration and not approved pre-treatment. Unnecessary addition of RBV was never used for G/P and VEL/SOF but was the only non-approved deviation for V/V/S.

SVR rates in "off-label" patients for G/P, VEL/SOF and V/V/S were 97% (37/38), 100% (10/10) and 100% (3/3), respectively.

For LDV/SOF the most frequent deviation to the label was unnecessary extension of treatment duration. However, for HCV GT 1, 4–6 infected patients irrespective of the cause of off-label use and other predictors like cirrhosis SVR rates remain high with 96–97% in comparison to 96–99% in patients treated in-label. For non-recommended use of LDV/SOF in HCV GT 2 and 3 infected patients SVR rates were low overall (88%) and in patients with shortened treatment duration (76%).

For GZR/EBR the most frequent deviation was not allowed pre-treatment. However, comparable SVR rates were observed for patients treated in- and off-label (98% versus 97%). No differences were observed with respect to the reason of off-label use, HCV subtype 1a versus 1b, baseline viral load and baseline RASs.

Conclusion: Most likely due to simplicity off-label administration of pangenotypic DAA regimen like G/P, VEL/SOF and V/V/S is rare and not associated with reduced SVR rates. Despite frequent inadvertent off-label use for LDV/SOF and GZR/EBR no reduced SVR rates were observed with exception to the use of LDV/SOF in HCV GT 2 and 3.

THU402

Real-world retreatment of HCV-infected patients with prior failure to direct acting antiviral therapy using sofosbuvir, velpatasvir and voxilaprevir

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Background and Aims: Sustained viral response (SVR) rates to first-line Direct Acting Antiviral (DAA) therapy routinely exceed 95%. However, a small number of patients require retreatment. Sofosbuvir, velpatasvir and voxilaprevir (SOF/VEL/VOX) is a potent DAA combination primarily used for the retreatment of patients failed by first line DAA therapies. Bourliere, et al showed in the POLARIS-1 phase 3 retreatment study of NS5A-experienced patients, SOF/VEL/VOX showed a very high SVR rate in genotype (GT)1 infected patients (97% SVR12; 0.7% virologic failure (VF)); however a higher virologic failure rate in GT3 patients was observed (95% SVR12; 5% VF). Here we evaluate virologic outcomes and the effects of resistance associated substitutions (RAS) in the largest real-world cohort of GT3 infected patients, retreated with SOF/VEL/VOX to date.
Method: Full-length genome, next-generation sequencing using target enrichment was performed on 215 patients following virologic failure with DAA treatment regimens in the UK. All patients were retreated with 8–24 weeks of SOF/VEL/VOX. HCV subtypes were assigned and RAS relevant to each genotype were identified (15% read cut-off) using a bespoke pipeline based on HCV-GLUE (hcv-glue.cvr.gla.ac.uk).

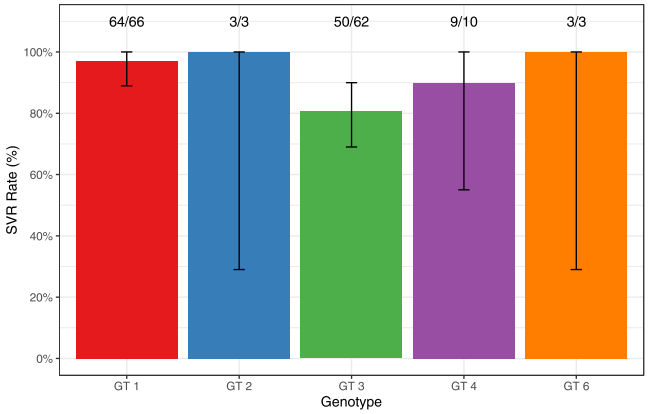

Figure 1: SVR12 rates for SOF/VEL/VOX against each HCV genotype. 95% confidence intervals shown by black lines.

Results: Of 215 patients, 35% were GT1a, 35% were GT3a, 5% GT1b, 2.5% GT4r, 2.5% GT3b, whilst 17 other subtypes were identified from genotypes 1,2,3,4 and 6. RAS against NS5A inhibitors were the most common (68%, n = 147) with the Y93H RAS being identified in 25% (n = 54) of sequences. Treatment outcomes are not currently known for 67 patients and 4 patients were lost to follow up, leaving 144 with known treatment outcomes. Of these, 40% (n = 58) had liver cirrhosis with 7% (n = 4) diagnosed as decompensated, 10% (n = 14) had HCC and 8% (n = 12) had received liver transplant prior to retreatment. The overall re-treatment SVR12 rate was 90% (129/144). The SVR rate for non-gt3 infected patients was 96% (79/82) whereas the SVR for GT3 infected patients was significantly lower 81% (50/602) ($p = 0.002$) (Figure 1). On univariate analysis, HCV GT3 ($p = 0.004$), cirrhosis ($p = 0.01$) and Y93H ($p = 0.03$) RAS were significantly associated with retreatment failure. However, in multivariate analysis only viral GT3 was associated with virologic failure ($p = 0.05$).
Conclusion: Although the overall rates of SVR in non-GT3 patients following retreatment with SOF/VEL/VOX are high, we show that in a large cohort of GT3 infected patients retreated with this regimen, SVR was only 81%. This may have important implications for elimination strategies in regions where GT3 dominates.

THU403

Resistance and phylogenetic analysis in HCV-2c infected patients within the Italian network VIRONET-C

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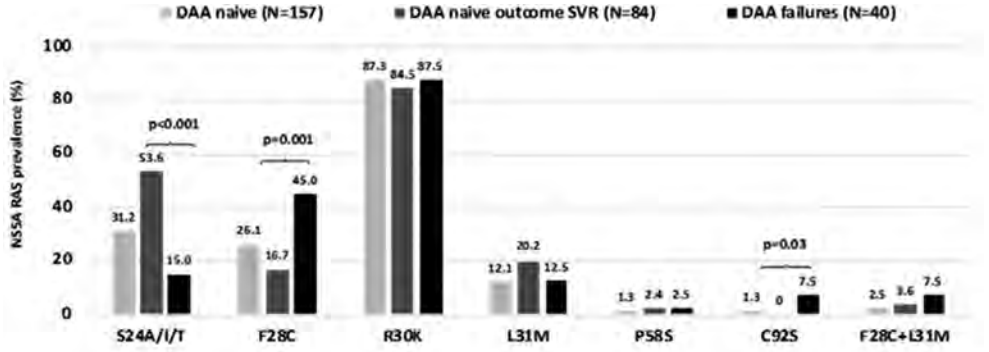
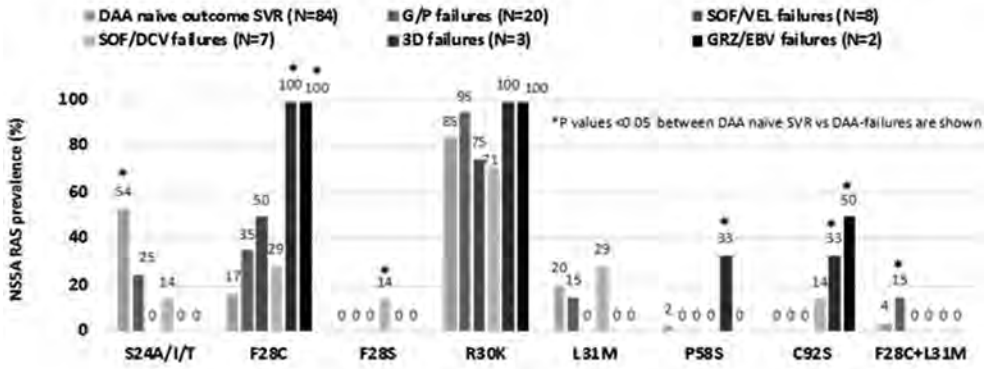
Background and Aims: HCV genotype 2 (GT2), particularly subtype c, is the second most prevalent GT in Italy after GT1b. Few data are available regarding the resistance-associated-substitutions (RASs) to direct acting antivirals (DAA) in GT2c. Therefore, the aim of this study





HCV GT2c clusters

ID	Clusters	Area	Outcome	GT	NS3 RAS	S24	F28C	L31M	R30K	P58S	C92S	N NS5A	HCV RNA LOG BL
47	1	Center	SVR	2c		S24A/S	1	1	1			4	5.9
96	1	Center	SVR	2c					1			1	6.3
205	2	North	NR 3D	2c	D168V		1		1	1		3	3.5
206	2	South	Relapse 3D	2c			1		1			2	5.3
136	3	North	SVR	2c		S24T		1	1			3	6.1
170	3	North	SVR	2c			1	1	1			3	4.0
141	4	North	SVR	2c					1			1	6.8
247	4	North	Relapse GP	2c			1		1			2	
147	5	North	SVR	2c		S24T			1			2	6.5
172	5	North	SVR	2c		S24T	1		1			3	4.9
184	5	North	SVR	2c		S24T			1			2	6.3
197	5	North	SVR	2c		S24T	1		1			3	3.5
133	6	North	SVR	2c		S24T		1	1			3	6.3
198	6	North	SVR	2c		S24T		1	1			3	6.6
134	7	North	SVR	2c					1			1	4.9
139	7	North	SVR	2c					1			1	5.9
149	8	North	SVR	2c		S24T		1	1			3	6.7
164	8	North	SVR	2c		S24T			1			2	5.1
189	8	North	SVR	2c					1			1	6.1
144	9	North	SVR	2c		S24T			1			2	4.9
146	9	North	SVR	2c		S24T		1	1			3	4.3
165	9	North	SVR	2c		S24T			1			2	6.9
179	10	North	SVR	2c		S24T			1			2	7.0
192	10	North	SVR	2c		S24T		1	1			3	6.0
194	10	North	SVR	2c		S24T		1	1			3	5.1
142	11	North	SVR	2c		S24I						1	7.2
161	11	North	SVR	2c		S24I						1	6.8

Figure: (abstract: **THU403**): Prevalence of NS5A resistance associated substitutions in DAA-naïves and DAA-failed & phylogenetic clusters in GT2c infected patients.

was to investigate the prevalence and role of RASs and presence of phylogenetic clusters in GT2c, in Italy.
Method: Within the Italian VIRONET-C network, a total of 248 GT2 infected patients (pts) (204 DAA-naïve and 44 NS5A-failed), were analyzed. Sanger-sequencing of NS3/NS5A/NS5B was performed following home-made protocols. RAS and polymorphisms in NS3 (N = 167) and NS5A sequences (N = 197) were analysed. Cluster analysis was performed on NS5A sequences by Bayesian analysis (posterior probability ≥ 0.98).
Results: The majority of pts were Italians (92%), males (56%) with a median (IQR) age of 69 years (54–78); 2.5% were HIV co-infected and 25% cirrhotics. Phylogenetic analysis classified sequences as GT2a-2b-2c (4%-<1%-96%), respectively. Interestingly, a total of 11 transmission clusters (7 with 2 sequences and 4 with >3 sequences) were identified among GT2c infected pts. In particular, 9 clusters involved 23 pts from Northern Italy (all SVR, except one), 1 pair from Center (both SVR) and 1 pair from Northern-Southern (both DAA-failed; Fig). 84 DAA-naïve pts with SVR and 40 DAA-failed with GT2c infection were treated with the following recommended regimens: glecaprevir (G)/pibrentasvir(P) (18/20), sofosbuvir(SOF)/velpatasvir (VEL)±ribavirin (RBV) (54/8), SOF/daclatasvir±RBV (12/7), while suboptimal regimens for misclassified genotype were Paritaprevir/r+Ombitasvir +Dasabuvir±RBV (N = 0/3), grazoprevir/elbasvir (N = 0/2).
Notably, a different distribution of specific NS5A RASs was found among DAA-SVR pts versus DAA-failed, particularly among those exposed to suboptimal regimens (Fig). Only the pattern F28C+L31M was statistically significant associated with G/P failures. No naïves nor no failed with GT2c infection showed Y93FHNRS RASs. Considering NS3, >95% of DAA-naïves and DAA-failed showed 80G and 56F. Notably, 4/25 (16%) GT2c NS3-failures showed D168A/V and/or F56H/Y never detected in DAA-naïve pts.
Conclusion: In this large Italian cohort of GT2 infected pts, the most prevalent subtype was the unusual subtype c. The majority of GT2c failures with recommended regimens did not show specific HCV RAS at failure. Further structural and phenotypic analyses should investigate the role of the common polymorphisms observed in GT2c.

THU404
Grazoprevir/elbasvir for treatment of hepatitis C virus genotype 4 post kidney transplant

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Background and Aims: Hepatitis C virus (HCV) infection affects about 150 million individuals worldwide and is a major cause of chronic hepatitis C, hepatocellular carcinoma, and liver cirrhosis leading to liver transplant or death. The overall prevalence of HCV in Saudi Arabia is estimated to fall between 0.3 to 1.1 percent. HCV genotype 4 was identified as the most prevalent genotype followed by genotype 1. Renal transplant recipients have a HCV infection rate of 5 to 15% in the developed countries, with higher rates reported in the developing world. Evidence suggests that the long-term graft and patient survival rates of HCV positive renal transplant recipients were significantly lower than that of HCV negative patients. There is however very limited data on the use of direct acting antivirals in patients with HCV genotype 4 post renal transplant. Our objective is to study the efficacy and safety of Grazoprevir/Elbasvir combination treatment without ribavirin in patients with HCV genotype 4 post renal transplant.
Method: It is a prospective, single arm, interventional, cohort study at King Faisal Specialist Hospital Riyadh that included all adult HCV genotype 4 infected patients post renal transplant with stable graft function. Patients received Grazoprevir/Elbasvir combination without ribavirin daily for 12 weeks. Patients co-infected with Hepatitis B Virus, Human Immunodeficiency Virus or has evidence of decompensated liver disease were excluded. Response was defined by sustained virologic response 12 weeks after completion of therapy (SVR 12).
Results: Nine patients with HCV genotype 4 infection post renal transplant were treated in our center. Three patients had mixed genotype 4 and 1 (33%). All patients (100%) were naïve to therapy. 2 had fibrosis score 0 (22%), 3 had Fibrosis score 1 (33%), 1 had Fibrosis score 2/3 (11%), and 3 had Fibrosis score 4 (33%). Week 4 HCV Polymerase chain reaction (PCR) was negative in all patients out of 9 with a treatment response of 100%. All patients completed the treatment period. SVR 12 was achieved in 100% of patients with no treatment failure or relapse. There was no any major or minor side effects during treatment. Renal function was stable during and after treatment period with no deterioration of graft function. The over all SVR 12 was 100%.
Conclusion: Grazoprevir/Elbasvir combination without ribavirin is an effective and safe treatment option for patients with HCV infection genotype 4 in the post renal transplant setting.

THU405
Drug - drug and drug - disease interactions in the treatment of hepatitis C in patients with liver cirrhosis: a single-center experience

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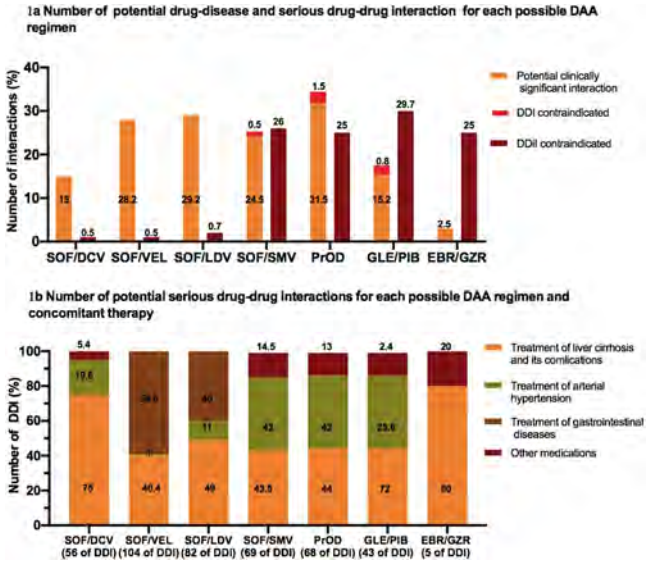
Background and Aims: Direct acting antivirals (DAAs) have a high rate of SVR with little side effects and short treatment duration. However, these agents can be involved in drug-drug (DDI) and drug-disease (DDiI) interactions, that can adversely impact the effectiveness and safety of treatment. The aim of study was to assess the prevalence of comorbidities, concomitant medications and the frequency of potential DDIs and DDiIs in patients with hepatitis C virus (HCV) related liver cirrhosis.
Method: Our observational non-interventionist study included 192 patients with HCV-related cirrhosis. Median patients age was 54 [29–72] years, 47% were male, 70.3% had a genotype 1 and 29.7% - Child - Pugh class B/C. We described predicted drug interactions with the concomitant drug and diseases based on data available at www.hep-druginteractions.org and prescribing information.
Results: Overall, 159 (83%) of patients in the study had comorbidities with mean number 2.6. Most common comorbidities were arterial hypertension (37.7%), gastritis (36.5%) and diabetes mellitus (24.5%). Two (1%) patients had a glomerular filtration rate <30 ml/min. Overall, 144 (75%) patients took at least one concomitant medication, ranging from 1 to 9 per patient. Beta-blockers (18.6%), gastrointestinal agents (18%), diuretics (15%) were most frequently used. Overall, 369 medications were prescribed, 30.5% of them - for management of liver cirrhosis and its complications (non-selective beta-blockers, diuretics, anticoagulants, antimicrobials). Protease inhibitors-containing regimens have shown a high frequency of dangerous DDiIs due to the presence of decompensated liver cirrhosis in a third of our patients (figure a). Overall, 44% of prescribed medications have demonstrated clinically significant or dangerous interactions with at least one of the DAA regimens (figure a). The contraindicated drugs

count for up 1.6% of the predicted interactions and included calcium channel blockers, statins, antimicrobials and direct oral anticoagulants. Other drugs induced clinically significant DDIs and also included beta-blockers, diuretics, angiotensin converting enzyme inhibitors, steroids. Proton pump inhibitors were responsible for many clinically relevant interactions with velpatasvir and ledipasvir due to high incidence of acid-related disorders in the patients in our cohort (figure b).



Conclusion: The majority of patients with liver cirrhosis are at risk for clinically relevant drug interactions due to high incidence of comorbidities and concomitant therapy. The potential for DDIs and DDIls is still an important consideration in determining an optimal DAA regimen and the adjustment of concomitant medications.

THU406

Integrated efficacy and safety analysis of GT1-6 treatment-naive, non-cirrhotic and compensated cirrhotic patients who received 8 weeks of glecaprevir/pibrentasvir

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Background and Aims: The once-daily, all-oral, fixed-dose direct-acting antiviral combination glecaprevir (developed by AbbVie and Enanta) and pibrentasvir (G/P) is approved for chronic hepatitis C virus (HCV) infection in adults with genotypes (GT) 1–6. In the US, G/P is approved for an 8-week duration in HCV GT1–6, treatment naïve (TN), non-cirrhotic (NC) and cirrhotic patients (CC). In Europe, 8 weeks is indicated for HCV GT1–6 TN NC, and TN CC with GT1, 2, 4–6. In GT3 TN CC, 12 weeks is still recommended. This integrated analysis of label-consistent data evaluates the efficacy and safety of G/P for 8 weeks in NC and CC, TN patients.
Method: Data were pooled from TN patients with HCV GT1–6, receiving current label-consistent
8-week G/P across 8 Phase 2 and 3 clinical trials. Analyses were in intention-to-treat (ITT) and modified ITT (mITT; excluding non-virologic failures) populations.
Results: The table shows baseline demographics. Rates of sustained virologic response at Post-treatment Week 12 (SVR12) for NC patients with HCV GT1–6 were 97.6% (883/905) in the ITT and 99.2% (883/890) in the mITT populations. In NC and CC patients with HCV GT1–6, SVR12 rates were 97.6% (1218/1248) in the ITT and 99.3% (1218/1226) in the mITT populations. The SVR12 rates for NC and CC patients with HCV GT 1–6, excluding CC GT3 patients, were 97.6% (1157/1185) and 99.4% (1157/1164) in the ITT and mITT populations, respectively. Across all 3 groups, SVR12 rates remained high regardless of GT (94.3–100%); the GT3 ITT SVR rate was 95.4% for each group. The percentage of patients experiencing adverse events (AEs) was similar for all 3 groups (58–62%). The 3 most frequent AEs in each group were headache, fatigue, and nausea. In all groups, serious AEs were reported in <3% of patients and AEs led to study drug discontinuation in <1% of patients.
Conclusion: These data support 8-week treatment with G/P in TN GT1–6 patients, regardless of cirrhosis status, thus simplifying pre-treatment assessments for the selection of one short duration for most patients.

Table: (abstract: THU406): Baseline demographics

n (%) or mean ±SD	G/P for 8 weeks		
	GT1–6, TN, NC (n = 905)	US Label GT1–6, TN, NC/CC (n = 1248)	EU Label GT1–6, TN, NC/CC (excl. CC GT3) (n = 1185)
Male	492 (54)	709 (57)	660 (56)
White	708 (78)	993 (80)	931 (79)
Age, years	50.3 ± 12.55	52.3 ± 12.47	52.4 ± 12.62
GT			
1	352 (39)	583 (47)	583 (49)
2	202 (22)	228 (18)	228 (19)
3	217 (24)	280 (22)	217 (18)
4/5/6	53 (6)/19 (2)/62 (7)	66 (5)/20 (2)/71 (6)	66 (6)/20 (2)/71 (6)
Cirrhosis	NA	343 (27)	280 (24)

THU407

Hepatitis C micro-elimination pilot strategy in Pakistani migrants in Catalonia through the implementation of a community intervention: interim results of the HepC-link study

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Background and Aims: Subjects from Pakistan living in Catalonia could have a high rate of hepatitis C virus (HCV) infection, and may have limited access to the health system. Therefore, it is necessary to design and evaluate strategies specifically targeting this collective to achieve HCV micro-elimination. The aim of this study was to implement and evaluate a community intervention that brings together education, screening and simplified access to treatment in this population.

Method: HepC-link is a prospective study with opportunistic sampling of 500 migrants from Pakistan in Barcelona city and metropolitan area. Recruitment was carried out in the community through individual or group strategies based on an educational game (HEPARJOC). Epidemiological data were collected and, if accepted, on-site rapid testing for HCV antibodies was performed. In the anti-HCV positive cases, a dried blood spot (DBS) sample was also collected on site for HCV-RNA testing in the laboratory. This result was delivered in a medical visit scheduled at the International Health Unit where a venous blood sample was obtained for analysis (including the HCV viral load and the FIB-4 fibrosis index). Viremic participants received antiviral treatment in the same Unit and were followed according to the standard of care until the sustained virological response. The degree of acceptability, prevalence (anti-HCV and HCV-RNA), detection of new cases, and referral and adherence to the healthcare system were evaluated.

Results: From March to October 2019, 373 participants (66.1% men, median age of 36 years (range, 18–66) and median of 6 years of residence in Spain (range, 0–28)) were recruited. Among all participants, 139 (37.3%) did not know what hepatitis C was. Thirty-six participants (9.7%) had previously been screened for HCV (17/36 in Spain); 11/373 (3.0%) reported a previous positive result, 7/11 had been treated and two were being followed up. The acceptability rate of the rapid test was 98.1% (366/373), 4.4% (16/366) had a positive result, and 43.8% (7/16) were unaware of having been infected with HCV. Of the total of anti-HCV positive cases, 93.8% (15/16) accepted the collection of the DBS sample, with 33.3% (5/15) of them being viremic cases (2/5 newly diagnosed), which represents a prevalence of viremic infection of 1.4% (5/366). Among the viremic cases, two have already started treatment within the intervention, one through routine care, and one has been lost to follow-up.

Conclusion: This community intervention has had an excellent acceptability among Pakistani migrants, and has reached both males and females with a limited awareness about hepatitis C, and most of whom had not been screened for HCV infection. The high prevalence observed so far (4.4% for antibodies and 1.4% for HCV-RNA), and the limited self-knowledge of their serological and viremic status against HCV justify a targeted screening in this group.

THU408

Characteristics of adults with difficult-to-treat hepatitis C virus genotype subtype 4r infection in Rwanda: a secondary analysis of a clinical trial in Sub-Saharan Africa (shared study)

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	GT4r participants (n = 48)	GT non-4r participants (n = 252)	P-value
Gender, female	29 (60.4%)	157 (62.3%)	0.81
Age, > 40	41 (85.4%)	235 (93.2%)	0.067
Primary school complete	24 (50.0%)	151 (59.9%)	0.20
Formal Employment	19 (39.6%)	89 (35.3%)	0.57
Monthly income ≥ $120 USD	17 (35.4%)	100 (39.7%)	0.58
Healthcare risks: blood transfusion, hospitalization, dental extraction, needlestick	34 (70.8%)	157 (62.3%)	0.26
Community risks: scarification, circumcision, tattoo, piercing	32 (66.7%)	144 (57.1%)	0.22
Cirrhosis (APRI>2 or ultrasound findings)	11 (22.9%)	23 (9.1%)	0.006
HCV RNA > 1,000,000 IU/mL	34 (70.8%)	113 (44.8%)	0.001
ALT > 40 IU/mL	29 (60.4%)	93 (36.9%)	0.002

Figure: (abstract: THU408): Sociodemographic, epidemiologic, and clinical characteristics of participants with HCV GT4r and GT non-4r (n = 300)

Background and Aims: In sub-Saharan Africa (SSA), there exist distinct HCV genotype (GT) subtypes that frequently harbour resistance associated substitutions to commonly used NS5A inhibitor-based DAA regimens. GT4r subtype, highly prevalent in Eastern and Central Africa and SSA immigrants, has demonstrated high rates of treatment failure. In a prospective trial of SOF/LDV in Rwanda, only 56% of participants with GT4r achieved SVR12. Without routine viral sequencing in SSA, it is important to identify sociodemographic, epidemiologic, and clinical characteristics that may predict GT4r infection and predict treatment failure.
Method: A secondary analysis was performed on data from 300 adults with HCV GT4 enrolled in a prospective trial assessing the safety and efficacy of SOF/LDV in Rwanda from February 6, 2017-September 18, 2017. GT subtype was determined by PCR amplification. Association between characteristics at enrolment and GT subtype were assessed by chi-squared analysis.
Results: Participants with GT4r had no significantly different sociodemographic characteristics, geographical origin, or HCV risk factors compared to non-GT4r participants (Table 1). Participants with GT4r were more likely to have baseline cirrhosis by APRI >2 or ultrasound (p = 0.006), viral load >1,000,000 IU/mL (p = 0.001), and ALT>40 IU/mL (p = 0.002).
Conclusion: Rwandan adults with GT4r were more likely to have high viral load or advanced liver disease compared to other GT4 subtypes. In the absence of advanced diagnostics to assess GT subtype, patients with these characteristics may warrant closer monitoring for treatment failure or alternative DAA regimens. More treatment experience with diverse DAA regimens is urgently needed for GT subtypes particular to this region.

THU409

The importance of medical specialists and services coordination to effectively treat hepatitis C infection in patients who inject drugs: the Trieste model of care

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Background and Aims: According to Italian data, people who inject drugs (PWID) have high prevalence of Hepatitis C Virus (HCV) infection (30–60%). PWID have potential inadequate access to directly acting antivirals (DAA) due to mistrust towards the healthcare specialists and services and their lack of coordination.
Method: Universal and free-of-charge infective screening is offered to PWID by the addiction treatment service (SERD). Patients are introduced to counseling where HCV risk behaviors and harm reduction policies are carefully explained. HCV antibody detection represents the first-line of screening. Antibody-positive patients were offered further testing to determine HCV-RNA and genotype. Besides, they were evaluated by abdominal ultrasound and liver elastography and then referred to: (1) the Infective Disease Department (adults and/or HIV-coinfected patients) or (2) the Liver Clinic (teenagers, young adults, and/or patients with higher degree of liver fibrosis) – where the medical specialist prescribes DAA.
Results: Between January 2015 and December 2018, 2475 PWID were screened, of which 1655 resulted positive for HCV-antibodies. Around 90% of HCV-antibody positive patients agreed to further testing, which resulted in detection of HCV-RNA in blood samples of 367 individuals. The most prevalent genotypes were 3 (51%, subtype 3a in 61%) and 1 (40%, subtype 1b in 57%). 255 individuals resulted eligible for DAA treatment, in particular 45 patients were referred to the liver clinic, whereas 210 to the infective disease department. 177 patients (69%) presented fibrosis F0-2 at the beginning of therapy, 30 (12%) had F3, and 29 (11%) had F4. 249 (97.6%) patients had a sustained viral response at 12 weeks (SVR12), while 2 were non-responders, 2 had relapsing infection, and 2 presented with reinfection.
Conclusion: Our HCV care model demonstrated how an effective addiction treatment service is fundamental in the delivery and supervision of HCV treatment in PWID. The goal of the system is to create a personalized and straightforward care process that appoints the complexity and vulnerability of these patients. Simplified, integrated, and more flexible plans that promote the therapeutic relationship between the patients with the medical and nursing personnel, allow (1) quicker access to treatment, (2) increased adherence to therapy, and (3) changes in risk behaviors, thus reducing reinfection rate and progressively decreasing virus prevalence in the target population.

THU410

The outcome of re-treatment of relapsed hepatitis C virus infection after direct acting antiviral treatment failure in resource-limited settings

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Background and Aims: Hepatitis C virus infection (HCV) is a public health concern. The mass scale up and uptake of treatment in Egypt with direct acting antiviral agents (DAAs) led to the identification of some treatment failures.
The aim of this study is to compare efficacy and safety of different combination regimens in re-treatment of HCV after failure of previous treatment and inaccessible resistance testing.
Method: This real-life prospective study included 86 chronic HCV infected patients who experienced failure of treatment out of 3000 who received DAAs at the viral hepatitis and research centre (Faculty of Medicine Ain shams Research Institute (MASRI) since 2018. 64% of the patients were males, with median age 50.2. Six patients were child B cirrhosis. They were re-treated using 3 combinations of DAA regimens. One group received PAR/OMB/SOF/RBV for 12 weeks, another group received SOF/DAC/SIM/RBV for 12 weeks and a third received SOF/DAC/RBV combinations for 24 weeks.
Response to different regimens was assessed by comparing sustained virologic response (SVR) of each group and also the effect of the previous failed regimen was observed as a possibility of being a risk factor. Safety was also assessed by monitoring the occurrence of adverse events.
The regimens used in this study were due to unavailability of other combination regimens as sofosbuvir, velpatasvir and voxilaprevir.
Results: Overall, SVR was achieved in 96.5% of the patients, 100% in those who received PAR/OMB/SOF/RBV, 98.1% in the SOF/DAC/SIM/RBV group and 71.4% among the SOF/DAC/RBV regimen group. Only three patients failed to achieve SVR, one of them had severe degree of fibrosis while two of them had moderate degree of fibrosis according to Fib 4 score. In general, all treatment regimens had comparable adverse events were mostly related to RBV as anaemia and hyperbilirubinemia.
Previous treatment used was a significant predictor to achieve to SVR. Patients who did not achieve SVR were previously treated with either SOF/INF or SOF/DAC.
Conclusion: In the absence of resistance testing, Sofosbuvir based combinations remain to be effective and safe alternative treatment regimens for retreating hepatitis C virus-infected patients who experienced previous failure of treatment. Additionally, the choice

of the first line of treatment has a significant role in treatment response.

THU411

Resistance-associated variants conferring quite a high level of resistance to all approved NS5A inhibitors in genotype 2 hepatitis C virus

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Background and Aims: Development of direct-acting antivirals (DAAs) has made anti-hepatitis C virus (HCV) treatment highly safe and effective. However, the emergence of resistant-associated variants (RAVs) after failure of DAA therapy affects retreatment outcomes. In particular, genotype 1 HCV with P32deletion has been reported to be highly resistant to all approved NS5A inhibitors. However, analysis of RAVs in genotype 2 HCV has been limited. Accordingly, in this study, we evaluated the roles of genotype 2 HCV variants in antiviral drug efficacy.
Method: We utilized HCV-2b/2a (JFH-1) chimeric virus (genotype 2a), which replicates more robustly than JFH-1. We constructed various genotype 2a JFH-1-based HCV cell culture systems with NS3 (D168E), NS5A (F28S, F28S/M31I, P32deletion, andY93H), and NS5B (S282 T) RAVs and analyzed the replication ability and sensitivity to various anti-HCV reagents.
Results: Genotype 2a-based HCV with NS5A-P32deletion could not replicate even in long-term cultures. Genotype 2a-based HCV with NS5A-F28S/M31I showed significantly higher replication ability than the wild-type strain, and replication could not be suppressed, even with high concentrations of NS5A inhibitors, including pibrentasvir and velpatasvir (<1000–10000 fold-resistance compared with the wild-type strain). However, genotype 2a-based HCV with NA5A-F28S/M31I was sensitive to HCV protease inhibitor, NS5B inhibitor, interferon-α, and ribavirin. Genotype 2a-based HCV with NS5B-S282 T was resistant to sofosbuvir, but was highly sensitive to ribavirin compared with the control.
Conclusion: When performing retreatment for genotype 2a HCV-infected patients who fail to respond to DAAs, the optimized retreatment should be chosen according to the sensitivity of the emerging RAVs to anti-HCV drugs.

THU412

A phase 2, open-label study of pan-genotype regimen of SH229 plus daclatasvir in Chinese patients with chronic hepatitis C virus infection

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Background and Aims: SH229 is a novel potent, pan-genotypic HCV NS5B polymerase inhibitor in development for the treatment of chronic HCV infection. During a 3-day monotherapy study in patients with HCV infection, SH229 was well-tolerated and resulted in median maximum HCV RNA reductions >3.8 $\log_{10}$ IU/mL at doses of 400, 600 and 800 mg once daily. Here we evaluate the efficacy and safety of SH229 in combination with daclatasvir (an HCV NS5A inhibitor) in Chinese patients infected with HCV genotype 1, 2, 3, or 6.
Method: In this open-label study, patients with chronic HCV infection were randomly assigned into three cohorts with a 1:1:1 ratio to receive 12 weeks of daclatasvir at a standard dose of 60 mg daily plus SH229 at a dose of 400 mg (Cohort A), 600 mg (Cohort B) or 800 mg (Cohort C) daily. Randomization was stratified by HCV genotype (1, 2, 3, and 6) and the presence or absence of cirrhosis at screening. Plasma samples were collected for HCV RNA quantification using Roche COBAS® AmpliPrep®/COBAS® TaqMan® HCV v2.0 test, which has a reported lower limit of quantification (LLOQ) of 15 IU/mL. The primary endpoint was a sustained virologic response 12 weeks after the end of treatment (SVR12).
Results: 124 patients were enrolled in the study, including 64 (51.6%) with HCV genotype 1, 31 (25.0%) with HCV genotype 2, 14 (11.3%) with HCV genotype 3, and 15 (12.1%) with genotype 6. 8.9% of patients had cirrhosis at baseline, 6.5% failed prior interferon-based therapy, and 88.7% had the IL28B CC allele. The median baseline HCV RNA was 6.3 log10 IU/mL, and 50.8% of patients had a baseline HCV RNA ≥ 200,000 IU/mL. The baseline disease characteristics are comparable among the treatment groups and no major differences are noted. As of Nov 19, 2019, 122 patients were available for post-treatment Week 12 assessments at this cut-off time. SVR12 was achieved in 92.5% (37/40), 95.2% (40/42), and 100% (40/40) of patients in Cohort A, B, and C, respectively. The overall SVR12 rate was 100% (62/62) among patients with HCV genotype 1, 100% (31/31) with genotype 2, 71.4% (10/14) with genotype 3, and 93.3% (14/15) with genotype 6. A similar number of patients experienced adverse events across three cohorts, and the majority of adverse events were mild to moderate in intensity. There were no discontinuations due to adverse events, and no treatment-related serious adverse events were reported.
Conclusion: Once-daily oral administration of SH229 plus daclatasvir were highly effective and safe in Chinese patients infected with HCV genotype 1, 2, 3, or 6, suggesting SH229 could be a promising drug candidate for HCV treatment in China irrespective of genotype.

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Health-related quality of life (HRQOL) before and after treatment of genotype 1 (GT1) infection with elbasvir/grazoprevir (EBR/GZR): results from the German hepatitis C registry (DHC-R)

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Background and Aims: Recent studies show that HRQOL improve during and after direct-acting antiviral (DAA) therapies for HCV infection. However, it remains unclear whether these findings can be generalized to patients (pts) treated in real-world as clinical trials enroll highly selected pts and typically under-represent important subgroups of the HCV population. The present analysis investigated

the impact of the regimen with EBR/GZR on HRQOL in pts treated for GT1 infection in German real-world.

Method: From 09/2016 until 06/2019, 1408 pts with GT1 infection were treated with EBR/GZR +/– RBV for 12 to 16 weeks in 130 medical practices and hospital outpatient departments. Pts were documented in the German Hepatitis C Registry (DHC-R). HRQOL was assessed by the 36-item short form health survey (SF-36). The present analysis was restricted to 257 pts with documented SF-36 data at baseline and 24 weeks of follow-up (FU) after end of treatment.

Results: 257 pts included in the present analysis showed the following characteristics: mean age 55 years, female gender 43%, GT1a 32%, GT1b 68%, BMI 26, elevated ALT 69%, elevated gamma-GT 54%, liver cirrhosis 21%. Overall, 98.4% (249/253) of pts infected with GT1 achieved a sustained virologic response (SVR) at 12/24 weeks post treatment with EBR/GZR. In all pts, all mean scores of the eight SF-36 domains improved slightly at 24 weeks of FU compared to baseline. However, pts experiences before and after treatment were heterogeneous in subgroups of interest. At baseline drug users under opioid substitution (OST), pts with chronic alcohol use and pts >70 years had lower scores than pts without any of these comorbidities. At 24 weeks of FU improvements in the SF-36 domains were more pronounced in OST pts and pts with chronic alcohol use and less pronounced in pts >70 years. While pts with alcohol use showed distinctive increases in role physical and mental health together with slight declines in other functions, OST pts had improvements in all domains, most distinctly in role physical, bodily pain, social functioning and role emotional (table).

Table: Mean SF-36 score changes before and after treatment

SF-36 domains	All pts N = 257	Pts without comorbidities N = 44	OST pts N = 31	Pts with alcohol use N = 9	Pts >70 N = 30
Physical functioning	74–78	84–90	76–83	79–77	59–63
Role physical	63–69	81–89	58–76	39–69	47–46
Bodily pain	70–76	85–87	66–84	77–74	57–68
General health	56–63	69–72	51–61	52–57	51–57
Vitality	47–55	55–64	41–50	44–52	45–49
Social functioning	75–80	86–88	64–79	69–75	72–74
Role emotional	69–76	86–87	59–76	52–59	54–59
Mental health	65–69	70–74	54–65	53–63	62–64

Conclusion: GT1 infected pts treated with EBR/GZR in German real-world show slight improvements in SF-36 domains post therapy. Heterogeneous experiences are observed in subgroups, ranging from less distinct changes in elderly pts to some notable score increases in pts with alcohol use and great improvements in OST pts.

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Second-generation DAAs for HCV: real-life efficacy in the resist-HCV cohort

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Background and Aims: RESIST-HCV (Rete Sicilia Selezione Terapia–HCV) registers all patients in Sicily with chronic HCV infection undergoing treatment with DAAs. This analysis aims to evaluate SVR rates of DAA-naïve patients to. second-generation regimens (Sofosbuvir plus Velpatasvir: SOF/VEL; Glecaprevir plus Pibrentasvir: GLE/PIB; Elbasvir/Grazoprevir: EBV/GRZ), in order to evaluate

Methods: We analyzed 4,087 patients who received treatment between March 2017 and December 2018 whose SVR12 data were available in the RESIST-HCV database by June 2019. Cirrhosis was diagnosed by liver stiffness ≥ 12 KPa (Fibroscan) and/or by presence of esophageal varices at endoscopy and/or by a liver biopsy with METAVIR stage 4 fibrosis.

	DAA regimes	Chronic hepatitis	Cirrhosis
Genotype 1a (436 patients)	SOF/VEL	203/205 (99%)	70/71 (98.6%)
	GLE/PIB	93/93 (100%)	7/7 (100%)
	EBV/GRZ	43/43 (100%)	11/11 (100%)
Genotype 1b (2,434 patients)	SOF/VEL	519/520 (99.8%)	297/303 (98%)
	GLE/PIB	408/410 (99.5%)	26/26 (100)
	EBV/GRZ	873/910 (95.9%)	251/265 (94.7%)
Genotype 2 (577 patients)	SOF/VEL	350/352 (99.4%)	72/72 (100%)
	GLE/PIB	147/148 (99.3%)	5/5 (100%)
Genotype 3 (332 patients)	SOF/VEL	175/179 (97.7%)	35/35 (100%)
	SOF/VOL + ribavirin	12/12 (100%)	27/27 (100%)
	GLE/PIB	63/64 (98.4%)	15/15 (100%)
Genotype 4 (171 patients)	SOF/VEL	65/65 (100%)	30/31 (96.7%)
	GLE/PIB	39/39 (100%)	1/1 (100%)
	EBV/GRZ	28/30 (93.3%)	8/8 (100%)

Results: By ITT analysis 95.1% of patients (3,878/4,078) achieved SVR. Overall, 125 patients (3.1%) did not complete the assigned therapy. Of them, 11 patients (0.3%) died for liver-related (5 patients) or unrelated (6 patients) causes while on treatment. Twenty patients (0.5%) discontinued treatment due to adverse events and 94 patients (2.2%) did not have virology available at end of therapy (ETR) or for SVR evaluation. Seventy-five patients (1.8%) did not achieve SVR: of them, 14 were still HCV-RNA positive at the end of therapy and 61 showed a virological relapse after ETR. By PP analysis 98.1% of patients (3878/3953) obtained an SVR. The rates of PP SVR according to HCV genotype (Gt) and stage of disease are reported Table 1. Patients with chronic hepatitis and Gt 1a, 1b, 2 or 4 obtained SVR rates higher than 99% when treated with pangenotypic regimes (SOF/VEL or GLE/PIB). SVR rates above 96% were obtained in patients with cirrhosis and Gt 1a,1b, 2 or 4 treated with SOF/VEL or GLE/PIB. Adding ribavirin to SOF/VEL in genotype 3 patients with chronic hepatitis or cirrhosis did not enhance the rate of SVR. Genotype 1b patients with chronic hepatitis or cirrhosis, when treated with EBV/GRZ had an SVR in 95.9% and 94.7% of cases, respectively, mostly due to post-ETR relapses.

Conclusions: Current DAA regimens, especially if pangenotypic, obtain response rates of at least 95% in a real-life situation. Adding ribavirin to SOF/VEL seems unnecessary in Gt3 patients, regardless of fibrosis.

THU415

Use of sofosbuvir based direct acting antiviral regimens is associated with reduced mortality in liver transplant candidates with hepatitis C

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Background and Aims: The role of sofosbuvir (SOF) based direct acting antivirals (DAAs) in waitlisted liver transplant candidates with Hepatitis C virus (HCV) is controversial, because of the concern that DAA use may disadvantage patients under the MELD system. Waitlist outcome data to date has been limited to select centers. The purpose of this study was to determine the prevalence of SOF containing DAA regimen use in liver transplant candidates in a nationwide registry and the associated impact on outcomes.
Method: Using the Scientific Registry of Transplant Recipients database, we examined all adult candidates on the national liver transplant waitlist from January 1, 2014 to December 31, 2017 waiting for their first transplant with HCV as the primary or secondary indication for listing. This cohort was linked to a national database of pharmacy claims, to identify patients treated with SOF containing regimens (sofosbuvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir) during the study period. Subjects were followed from listing date or January 1, 2014 if they were listed before the study period until the first occurrence of removal from the waitlist, transplant, death, or December 31, 2017. The final cohort consisted of 1420 subjects. The SOF treated group was compared to a matched historical cohort of candidates waitlisted from January 1, 2010 to December 31, 2013 who were not treated with SOF based regimens. The groups were matched on several factors using incidence density without replacement sampling of 1 case up to 3 controls. Both univariate Cox proportional hazards models and cumulative incidence curves were done using competing risks methodology.

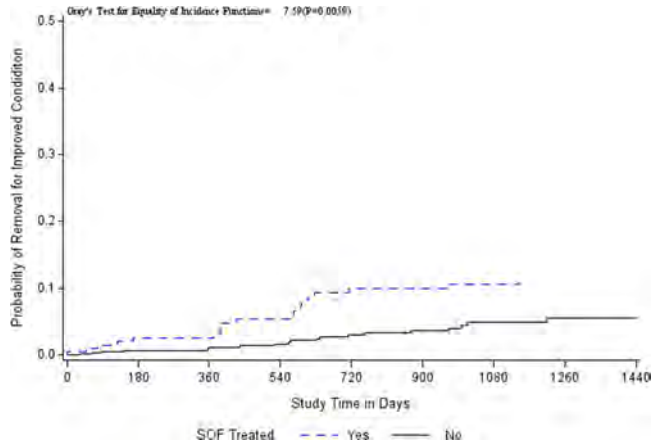

Figure: Removal from the liver transplant waiting list due to condition improved, according to exposure to SOF containing DAA.

Results: During the study period, 208 patients (14.6%) were treated with a SOF containing DAA regimen during liver transplant listing. There were 787 subjects in the matched cohort. Treatment with SOF based regimens was associated with a lower risk of all-cause mortality compared to non-treatment (HR 0.47, 95% CI 0.26–0.83, P = 0.0094). Patients treated with SOF based regimens were more likely to be removed from the waitlist due to improved condition compared to untreated subjects (HR 2.65, 95% CI 1.41–4.99, P = 0.0025). Liver transplant incidence (HR 1.02, 95% CI 0.78–1.34, P = 0.8719) and removal from the waitlist due to worsened condition (HR 0.84, 95% CI 0.50–1.40, P = 0.4941) did not differ between SOF treated and untreated groups.
Conclusion: In a contemporary national cohort, only a minority of waitlisted HCV positive liver transplant candidates were treated with SOF containing DAAs. However, SOF use was associated with reduced all-cause mortality and increased removal from the waitlist due to improved condition which suggests that HCV treatment should be considered in all HCV infected liver transplant candidates.

THU416

Factors associated with efficacy of retreatment with grecaprevir/pibrentasvir therapy in prior DAA failed patients - nationwide multicenter study in Japan

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Background and Aims: To identify factors associated with the efficacy of retreatment with grecaprevir/pibrentasvir (GLE/PIB) therapy in patients who failed prior DAA therapy.
Method: This was a nation-wide multicenter study involving 83 regional core centers for the treatment of liver disease and related hospitals. A total of 526 patients who failed prior DAA therapy and retreated with GLE/PIB were registered. Serum was obtained before GLE/PIB therapy and the RAS in NS3/NS5A region was determined by population sequencing. Factors associated with SVR12 were analyzed.
Results: The overall SVR12 rate was 96.5%; the SVR12 rate of genotype 1a, 1b, 2a, 2b patients was 100%, 96.5%, 100% and 100%, respectively. Among the genotype-1b patients, the SVR12 rate in 4 patients with P32deletion RAS in NS5A region was 25%, which was significantly lower than 97% of patients without this unique RAS ($p < 0.01$). Among patients without P32deletion RAS, presence of A92 K RAS in NS5A (odds ratio 15.3, 95% confidence interval 2.3–101, $p < 0.01$), R30H in NS5A (OR 9.1, 95%CI 1.8–46, $p < 0.01$), prior failure of multiple DAA regimens (OR 8.3, 95%CI 1.9–37, $p < 0.01$), and age over 76 (OR 4.5, 95% CI 1.2–17, $p = 0.03$) independently affected SVR. The SVR12 was 99% in 193 patients who had none of the above four factors, whereas it was 97% in 92 patients who had only one factor, and 76% in 21 patients who had 2–3 factors.
Conclusion: This nation-wide study revealed high rate of SVR by retreatment with GLE/PIB. The unique RAS P32deletion in NS5A significantly attenuated the efficacy. Other than this unique RAS, R30H RAS in NS5A, Y92 K in NS5A, prior failure of multiple DAA regimens, and age were factors to lower SVR rates. In patients without these factors, the rate of SVR was 99%.

THU417

Impact of the universal access to direct-acting antivirals in the profile of hepatitis C treated patients

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Background and Aims: Treatment with direct-acting antivirals (DAAs) was limited to patients with advanced fibrosis until 2017. Since then, access to DAAs was allowed to all subjects with chronic hepatitis C (CHC), regardless of the degree of fibrosis. Our aim was to analyse the impact of universal access to DAAs in the profile of subjects treated for CHC.
Method: Retrospective study based on the pharmacy register of all patients with CHC treated during two periods: restrictions (2014–2016) and universal access (2017–2019). Baseline clinical and virological characteristics, type of therapy and Sustained Virological response (SVR) were collected.
Results: 2,384 combinations of interferon-free oral DAAs were administered to 2,327 patients with CHC within these periods. The percentage of patients with advanced fibrosis (F3-F4) receiving therapy significantly decreased over time, although 23% of treated subjects in 2019 had significant fibrosis and 2% were decompensated. Baseline characteristics of subjects treated during each period are shown in the table. An increase in treated HIV-infected patients was observed, probably due to lower interactions with the new DAAs

Table: (abstract: THU417)

	Period with restrictions 2014–2016 (n = 1094)	Universal Access Period 2017–2019 (n = 1290)	Total (n = 2384)	
Male	613 (56%)	716 (56%)	1329 (56%)	p = 0.8
Age (years)	61 ± 13	57 ± 14	59 ± 14	p < 0.001
Fibrosis				p < 0.001
F0-F1	60 (6%)	538 (42%)	598 (25%)	
F2	241 (22%)	405 (31%)	646 (27%)	
F3	253 (23%)	154 (12%)	407 (17%)	
F4	540 (49%)	193 (15%)	733 (31%)	
Decompensated cirrhosis	38 (4%)	25 (2%)	63 (3%)	p = 0.2
Hepatocarcinoma	17 (2%)	4 (0.3%)	21 (1%)	p < 0.001
Liver transplant	52 (5%)	21 (2%)	73 (3%)	p < 0.001
HIV Coinfection	116 (11%)	238 (19%)	354 (15%)	p = 0.002
Genotype 1b	693 (63%)	558 (43%)	1251 (53%)	p < 0.001
Non- pangenotypic DAAs	1094 (100%)	605 (47%)	1709 (71%)	
Pangenotypic DAAs	–	675 (53%)	675 (29%)	
SVR 12	782/820 (95%)	983/1015 (97%)	1765/1835 (96%)	p = 0.1

Median, SD; n (%).
DAAs, Direct-Acting Antivirals. SVR12, Sustained virological response at week 12.

combinations. Genotype 1b was the most prevalent (53%) in the first period and decreased in the second period, due to an increase of patients infected by GT 1a, 3 and 4. Seven patients relapsed after DAA and were retreated with SOF/VEL/VOX, all of them achieving SVR. Pangenotypic regimens used in the second period slightly increased SVR rates.
Conclusion: Despite universal access to high efficacy pangenotypic DAAs combinations, 23% of patients treated in 2019 still had advanced fibrosis. This result highlights the need to improve and increase screening and linkage to care in order to eliminate HCV infection.

THU418

Hepatitis C therapy with grazoprevir/elbasvir and glecaprevir/pibrentasvir in patients with advanced chronic kidney disease - data from the German hepatitis C-registry (DHC-R)

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Background and Aims: Grazoprevir/elbasvir (EBR/GZR) and glecaprevir/pibrentasvir (G/P) are the two licensed treatment options with direct antiviral agents (DAA) for patients with chronic hepatitis C virus (HCV) infection and a baseline glomerular filtration rate (GFR) <30 ml/min. Real world data in this special patient population is sparse so far. Thus, we analyzed safety and effectiveness data within the German Hepatitis C-Registry (DHC-R).
Method: The DHC-R is a prospective national real-world registry including about 16,500 chronic hepatitis C patients recruited by more than 250 centers. Data were analyzed as of Jun 30, 2019. The analysis is based on 2,773 patients with documented GFR at baseline treated with EBR/GZR (N = 1,041), EBR/GZR + ribavirin (N = 53) and G/P (N = 1,679), respectively. For the per protocol analysis, non-adherent patients, patients with missing data and patients lost to follow-up were excluded.
Results: The baseline characteristics of the total study cohort were as follows: (70%/4%/21%/5% HCV-genotype 1/2/3/4; 64.7% male; age 50 ± 14 years, 96% Caucasian, 83% treatment-naïve,12% cirrhosis). 94 (3.4%) patients with baseline GFR <30 ml/min initiated antiviral therapy with EBR/GZR (N = 57), EBR/GZR + ribavirin (N = 4), or G/P (N

	End of treatment GFR			
Baseline GFR	**0-15**	**>15-30**	**>30-60**	**>60**
0-15 (n=79)	97.5% (n=77)	1.3% (n=1)	0	1.3% (n=1)
>15-30 (n=7)	14.3% (n=1)	57.1% (n=4)	14.3% (n=1)	14.3% (n=1)
>30-60 (n=83)	0	3.6% (n=3)	65.1% (n=54)	31.3% (n=26)
>60 (n=1,894)	0	0	2.4% (n=46)	97.6% (n=1,848)

Patients with documented GFR at baseline and end of treatment were considered in this analysis (N=2,063).

Figure: (abstract: **THU418**): Comparison between baseline and end-of-treatment glomerular filtration rate.

= 33). They suffered significantly more frequent from diabetes mellitus, hypertension, and coronary heart disease than individuals with GFR >30 ml/min and showed the following baseline characteristics: 78%/3%/13%/5% HCV-genotype 1/2/3/4; 13% cirrhosis; 81% treatment-naïve. Antiviral therapy was associated with a GFR improvement in 30/2,063 (1.5%) individuals, a deterioration to GFR <30 ml/min occurred in in 3/2,063 (0.1%) patients (Table 1). Adverse events (AE) occurred in 32.3% of patients with GFR <30 ml/min vs. 30% of cases with GFR >30 ml/min. Serious adverse events were significantly more frequent in individuals with GFR < 30 ml/min (7.5% vs. 1.4%), but unrelated to antiviral therapy in six cases. One patient suffered from a cholestatic hepatitis possibly related to EBR/GZR. Treatment discontinuation due to (serious) AE occurred in no patient with GFR <30 and in 0.1% of patients with GFR >30 ml/min. Per-Protocol overall sustained virologic response rates (SVR12) did not differ significantly between cases with GFR < 30 vs. >30 ml/min (99% vs. 99%).

Conclusion: EBR/GZR and G/P show a favorable safety profile and high antiviral efficacy in patients with chronic hepatitis C and a GFR < 30 ml/min.

THU419

HCV in the Australian primary care setting: real-world effectiveness of 12 weeks of sofosbuvir/velpatasvir for the treatment of chronic hepatitis C

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Background and Aims: The World Health Organization has set HCV elimination targets to be achieved by 2030. The availability of pangenotypic, panfibrotic direct-acting antiviral drugs, simplification of treatment and management, and decentralization of patient care are key to reaching these targets. In phase 3 clinical trials and multiple large real-world data cohorts, sofosbuvir/velpatasvir (SOF/VEL) is a simple pangenotypic, panfibrotic, single tablet regimen, showing high sustained virologic response (SVR) rates across all genotypes and fibrosis stages with favorable safety and tolerability. In Australia, over 39% of HCV treatment are initiated in primary care but limited clinical outcome data are available in this setting. This real-world data cohort assesses the effectiveness of a 12-week SOF/VEL regimen in treating chronic HCV patients exclusively in primary care.

Method: Data from seven primary care clinic cohorts are included. Patients enrolled in the cohorts were treated according to local standards of clinical care. Data on HCV patients who were treated with 12 weeks of SOF/VEL before July 2019 were extracted from each cohort database, excluding patients with a history of decompensation, prior exposure to an NS5A inhibitor, treatment duration >12 weeks or concomitant ribavirin use. Demographics, reasons for non-SVR and model of care utilized were assessed. SVR (≥12 weeks after end-of-treatment) was assessed for all patients with virologic outcome data available at the time of abstract submission.

Results: SOF/VEL treatment initiation was identified for 301 patients, with a median age of 43 (range 19–67) years. 42% of patients reported recent injecting drug use, 2% were treatment-experienced and 7% had compensated cirrhosis. All patients were initiated on SOF/VEL in primary care by a mixture of general practitioner (GP)-led and nurse-led clinics. SVR results were available for 159 patients, with a SVR of 97%. For 142 patients, SVR was not available due to non-virological reasons including loss to follow-up (LTFU). Detailed analyses of the virological and non-virological reasons for not achieving SVR will be available for the full cohort at the conference

Conclusion: A 12-week pangenotypic and panfibrotic treatment regimen of SOF/VEL offers a simple treatment regimen with high SVR12 rates of 97% in chronic HCV patients treated in GP or nurse-led clinics in Australia. However, measures should be taken to decrease LTFU of patients. This multi-center cohort is one of the first to show the feasibility and effectiveness of treating chronic HCV patients with SOF/VEL in the primary care setting, in line with the recent AASLD/APASL/EASL/ALEH call to action for HCV elimination.

THU420

Effectiveness of 8 weeks of glecaprevir/pibrentasvir in treatment-naive hepatitis C patients with liver cirrhosis: results from the real-world Spanish Hepa-C registry

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Background and Aims: Glecaprevir/pibrentasvir (G/P) is a pangenotypic antiviral regimen that allows hepatitis C virus infection (HCV) cure rates above 95%. The recommended duration of treatment in naive patients with compensated liver cirrhosis was 12 weeks. Recently, the Expedition-8 study showed that in this subgroup of patients, G/P treatment can be reduced to 8 weeks without losing efficacy (Brown RS et al, J Hepatol 2019), but results are unknown under real clinical practice conditions.

Method: Multicenter observational study of consecutive HCV patients treated with G/P under real clinical practice conditions in the Spanish HepaC registry between September 2017 and March 2019, who reached 12 weeks follow-up assessment of sustained virological response (SVR12). Inclusion criteria were genotype (GT) 1-6, treatment-naïve and compensated liver cirrhosis. Patients with HIV-HCV coinfection were excluded. Baseline characteristics of the patients and SVR12 were assessed according to the duration of treatment (8 or 12 weeks).

Table: (abstract: THU420): Baseline characteristics of patients treated with G/P for 8 vs. 12 weeks

		G/P treatment duration				
		8 weeks		12 weeks		p
		n	%	n	%	
Gender	Male	9	64.29%	60	60.00%	NS
	Female	5	35.71%	40	40.00%	NS
Race	Caucasian	13	92.86%	75	75.00%	NS
	Others/NA	1	7.14%	25	25.00%	NS
PWID	no	11	78.57%	71	71.00%	NS
	yes	3	21.43%	29	29.00%	NS
HBV	no	14	100.00%	99	99.00%	NS
	yes	0	0.00%	1	1.00%	NS
HCV genotype	NA	0	0.00%	3	3.00%	NS
	1	12	85.71%	63	63.00%	NS
	2	0	0.00%	2	2.00%	NS
	3	1	7.14%	25	25.00%	NS
	4	1	7.14%	7	7.00%	NS
Child-Pugh	A5	11	78.57%	68	68.00%	NS
	A6	1	7.14%	10	10.00%	NS
	A (score NA)	2	14.29%	20	20.00%	NS
	B7	0	0.00%	2	2.00%	NS
		n	Median (IQR)	n	Median (IQR)	
Liver Elastography (Kpa)		14	21.9 (15.7–31.8)	92	17 (14.9–23.4)	NS
		n	Mean (CI95)	n	Mean (CI95)	
Age (years)		14	61.89 (54.84–68.94)	100	58.53 (55.97–61.08)	NS
MDRD4 (ml/min)		13	98.62 (86.63–110.62)	76	92.71 (83.29–102.14)	NS
Bilirubin (mg/dL)		14	0.74 (0.59–0.88)	87	0.93 (0.74–1.11)	NS
Albumin (g/dL)		13	4.13 (3.9–4.35)	90	4.12 (4.01–4.23)	NS
INR		11	1.03 (0.99–1.07)	78	1.09 (1.06–1.12)	NS
Platelet count (x10^9)		14	155 (128.63–181.37)	99	148.31 (135.09–161.53)	NS

Results: 114 naive patients with cirrhosis received G/P treatment, 14 for 8 weeks and 100 for 12 weeks. 60.5% were males, with a mean age of 59 (31–89) years and 26% were infected with GT3. 69.3% had an A5 Child-Pugh score, 9.6% A6 and 1.76% B7. No differences in baseline characteristics were observed among patients treated 8 or 12 weeks (table). SVR12 was achieved in the 14 patients treated 8 weeks and in 98/100 treated 12 weeks. The two virological failures, both GT1, were due to viral relapse and a non-responder, respectively.
Conclusion: Preliminary results of the HepaC cohort show a high effectiveness of G/P treatment for 8 weeks in HCV treatment-naïve patients with compensated liver cirrhosis, being similar to that observed in patients treated for 12 weeks.

THU421

Baseline features of hepatitis C patients associated to prescription of pangenotypic antiviral treatments: results from the real-world Spanish Hepa-C registry

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Background and Aims: Glecaprevir/pibrentasvir (G/P) and sofosbuvir/velpatasvir (SOF/VEL) are the first line pangenotypic regimens available to treat hepatitis C virus infection (HCV). In Spain, the choice of SOL/VEL vs G/P relies on the physician, since costs are similar and access to care is universal. We investigated how patient baseline characteristics may influence the decision process leading to indicate

a pangenotypic HCV treatment in the real-world setting, and their impact on SVR.

Method: we performed a retrospective analysis of patients with hepatitis C who started treatment with G/P or SOF/VEL between April 2017 and September 2019, and were included at the multicenter Spanish registry HepaC. We developed a multivariable logistic regression analysis, including clinical and virological variables, predicting the antiviral treatment of choice. A second model was developed to evaluate the potential impact of this choice on SVR.

Results: 4093 patients were included, 2402 received G/P and 1691 SOF/VEL. Different prescription patterns were found. Liver cirrhosis, former/current drug use, asian ethnicity, treatment with proton pump inhibitors or oral anticoagulants, and HCV genotype (GT) 2 and 3 were associated to the use of SOF/VEL; GT1, caucasian ethnicity and glomerular filtration rate below 45 ml/min, including hemodialysis, were associated to G/P (table).

Table:: Factors associated to the use of G/P vs. SOF/VEL

		OR	CI 95%
Race	Caucasian (n = 3358)	1.0	
	Afrocaribbean (n = 14)	0.9	0.3–2.7
	Asian (n = 20)	0.3	0.1–1
	Arab (n = 37)	1.4	0.7–3
	Latino (n = 44)	1.2	0.6–2.3
	Hindu (n = 25)	2.1	0.9–5
	Other (n = 49)	2.0	1–3.9
	Unknown (n = 546)	2.0	1.2–3.4
Haemodialysis	No (n = 4073)	1.0	
	Yes (n = 20)	6.3	1.3–31
MDRD4	>45 (n = 3399)	1.0	
	≤ 45 (n = 78)	7.3	3.7–14.5
	NA (n = 616)	1.0	0.6–1.7
PWIDs	No (n = 3145)	1.0	
	Yes (n = 948)	0.7	0.6–0.8
Liver decompensation	No (n = 4006)	1.0	
	Yes (n = 87)	0.1	0–0.3
Cirrhosis	No (n = 3525)	1.0	
	Yes (n = 568)	0.5	0.4–0.6
Oral antiacoagulation	No (n = 4017)	1.0	
	Taking (n = 76)	0.4	0.2–0.6
Proton Pump Inhibitor	No (n = 3563)	1.0	
	Taking (n = 530)	0.6	0.5–0.8
Liver elastography	F1–2 (n = 3086)	1.0	
	F3–4 (n = 887)	0.5	0.4–0.6
	NA (n = 161)	0.5	0.4–0.8
Genotype	1 (n = 2455)	1.0	
	2 (n = 249)	0.3	0.2–0.3
	3 (n = 929)	0.2	0.2–0.2
	Other (n = 460)	0.9	0.7–1.2

Overall, SVR was 90.9% in G/P patients (virological failure 1%, lost to follow-up 8.1%) and 90.0% in SOF/VEL (virological failure 1.8%, lost to follow-up 8.2%). The independent predictors of virological failure were male gender (OR = 2.9 CI95% 1.4–6.2), cirrhosis (OR = 2.1, CI95% 1.1–3.8), GT2 (OR = 3.1, CI95% 1.1–8.7) and GT3 (OR = 3.4, CI95% 1.7–6.5); but not the specific antiviral treatment

Conclusion: in the setting of an unrestricted access to HCV therapies, baseline characteristics of patients may influence the selection of the antiviral regimen. SVR rates were very high and independent of treatment regimen; non response was associated to male gender, liver cirrhosis and HCV genotypes 2 and 3.

THU422

The English hepatitis C registry shows only a modest effect from non-completion of directly-acting antivirals for hepatitis C: SVR rates over 80% in genotype 1, 2 or 3 HCV if more than one third of planned treatment is completed

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Background and Aims: Until late 2019, DAA treatment funded by NHS England was limited to one treatment course per patient unless virological failure occurred.

The English national hepatitis C registry contains demographic, clinical and therapeutic data on every person in England known to have been treated for hepatitis C.

We aimed to quantify the effect of non-completion of a planned course of directly acting antiviral treatment.

Method: Sustained virological response (SVR) rates for patients who received a valid treatment for their genotype and were scheduled to finish treatment by 22 August 2018 were calculated from anonymised data. Odds ratios for SVR when treatment was completed or not were calculated using multivariable logistic regression to allow for confounding factors including age, gender, ethnicity, disease stage, treatment regimen and presence of HCC.

Results: Actual and planned treatment durations were recorded for 98.54% (14,391/14,603) of patients with an outcome 12 weeks after treatment. 4.38% (631/14,391) of these patients did not complete treatment.

Overall, patients who did not complete the planned treatment duration had a significantly lower SVR rate (80.67% (95% CI 77.45% to 83.60%)) than those who did (96.47% (95%CI 96.15% to 96.78%)). There was a trend for increasing SVR rate with increased proportion of treatment completed. If at least one third of treatment was completed, SVR rates for genotypes 1, 2 or 3 were over 80% and 69.23% for genotype 4.

Significantly more patients treated for genotype 1 HCV with 16 weeks of Elbasvir/Grazoprevir and Ribavirin did not complete treatment than in any other regimen (17.66% cf 1.90% to 4.85%, n = 145/821, p < 0.001). Adjusted odds ratios for SVR for genotype 1 and genotype 3 for non-completion of planned treatment compared to completion of planned treatment were 0.149 (95% CI 0.107 to 0.209) and 0.102 (95% CI 0.062 to 0.168) respectively.

Conclusion: Rates of treatment non-completion were low apart from patients with genotype 1 HCV treated with Elbasvir/Grazoprevir and Ribavirin for 16 weeks. Non-completion of the planned treatment duration was associated with significantly lower SVR rates overall. However, a plateau effect was seen with SVR rates over 80% in patients with genotype 1 or 3 who completed at least one third of planned treatment.

THU423

Evolution of hepatitis C virus genotype 1a vs 1b distribution reflects profound changes in HCV epidemiology in Germany - analysis of 17,093 patients from five consecutive registries including the German hepatitis C-registry (DHC-R)

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Background and Aims: Hepatitis C virus (HCV) genotype (GT) 1 is the most common HCV GT in Western and Central Europe. Overall, HCV GT 1a is found more frequently in persons who have acquired HCV by drug use while HCV GT 1b has frequently been transmitted by transfusion of blood products before 1992. HCV GT 1 subtypes show different responses to some of the approved direct acting antivirals which still has relevance as, e.g. elbasvir/grazoprevir is widely used in some European countries. A more detailed knowledge on the evolution of HCV GT 1a vs. 1b would lead to a better understanding of HCV epidemiology which could have consequences for HCV elimination strategies.
Method: The present analysis is based on five German non-interventional registry studies and comprises data on 17,093 HCV-GT1 patients documented between 2004 and 2018 [ML17071, ML19464, ML21645, ML25724 (Peginterferon alfa-2a® non-interventional study, PAN) and the German Hepatitis C-Registry (DHC-R)]. ML17071, ML19464, ML21645 and PAN were initially sponsored by Roche Pharma AG. In 2014, these data were transferred in anonymous form to the German Liver Foundation. Leberstiftungs-GmbH Deutschland initiated the DHC-R which currently includes about 16,500 patients.
Results: Overall, 7,662 patients were infected with HCV GT 1a and 9,431 patients with HCV GT 1b. GT 1a patients were younger (46.5 years vs. 51.2 years) and more often male (70% vs. 52%). Previous or ongoing drug abuse was documented more frequently for GT1a patients throughout the study periods with highest frequencies in the most recent period (2017–2018; 44% for GT1a and 10.3% for GT1b). Until 2013, more GT1b than GT1a infected patients were obese and had diabetes mellitus while the proportion of patients with liver cirrhosis did not differ between these subgenotypes. A significant change in the GT1a/1b ratio was observed over time in men with less than 40% being infected with GT1a in 2004–2007 and about 60% in 2017/2018. In contrast, only 28–38% of women had GT1a infection throughout all study periods. There were no regional differences within Germany in HCV GT1a/1b distribution despite a higher proportion of GT1b infected women in eastern Germany in 2004–2007 (86%).
Conclusion: A marked increase of GT1a infection associated with drug use was observed in men but not women in Germany between 2004 and 2018. Metabolic comorbidities such as overweight and diabetes mellitus were associated with HCV GT 1b infected women.

THU424

The quetiapine question: management strategies for drug-drug interactions with antipsychotics and direct acting antivirals; a multicentre review

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Background and Aims: Patients with mental illness are known to have higher prevalence of hepatitis C Virus (HCV). Direct Acting Antivirals (DAA) have enabled treatment for patients previously excluded due to psychiatric co-morbidities. However, some DAA may result in Drug Drug Interactions (DDI) with antipsychotics (AP) predominantly due to mild CYP3A4 or Pgp inhibition. Although many DAA/AP combinations are classed as green (no interaction expected) by University of Liverpool www.hep-druginteractions.org quetiapine, paliperidone and aripiprazole are as classed amber suggesting use with caution. This may result in increased levels of AP with subsequent toxicities, eg prolonged QTc interval, extrapyramidal or sedation. These could be further potentiated in presence of cirrhosis. The clinical significance of these DDI based on predictive pharmacokinetics is unknown. Management may include dose adjustment/change of AP, change to DAA or clinical monitoring, including ECG. We sought to describe characteristics of the patient cohort and management strategies of this DDI.
Method: Patients treated with DAA and co-prescribed quetiapine, aripiprazole or paliperidone from April 17-March 19 were identified in 5 treatment centres in Scotland. Data was collected on drugs prescribed, presence of cirrhosis, Adverse Drug Reactions (ADR) and virologic outcome. DAA choice was led by national guideline. Management of DDI was coded as: no action needed (NO), continue AP with clinical monitoring (CM), continue AP with dose reduction (DR), switch to alternative AP or DAA (SA/SD), or continue combination with ECG monitoring (ECG).
Results: 183 patients were identified, mean age 42.7 years (SD 9.4), male 123 (67.2%), F4 25 (13.7%). 72 (39.3%) patients had DDI categorised as green, therefore no action needed (NO). Of 111 (60.7%) amber DDI, management was; CM 67 (60.3%), DR 3 (3.3%), SD 26 (23.4%), ECG 15(13.5%) and ADR were reported in 8 patients (7.2%). Per protocol SVR12 was 97.6% (excluding 17 lost to follow up). Co-prescription of other QTc prolonging drugs was seen in 74 patients. Further breakdown will be presented.
Conclusion: Clinical monitoring was the most common strategy and minimal ADR were reported. Excellent virologic results were achieved. This data supports the use of all DAA regimens in the majority of patients prescribed these combinations. An individual approach can identify those few patients who require additional input such as use of high dose antipsychotics, other QTc prolonging drugs or cirrhosis. This data should reassure prescribers and ensure patients in this vulnerable group have access to safe and effective treatment.

THU425

Identification of patients with compensated cirrhosis who can safely use protease inhibitor-based therapy for HCV infection

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Background and Aims: Direct-acting antivirals (DAAs) are now widely used as treatment for chronic HCV in patients with compensated and decompensated cirrhosis. Based on reported decompensation events during treatment, advisories about use of protease inhibitors (PI) have been issued. Simple identification of patients with cirrhosis with a very low risk of decompensation during treatment who can safely use PI-based therapy would be very helpful.

Method: Retrospective cohort study including all consecutively chronic hepatitis C (HCV) patients treated with DAAs in 4 international hepatology clinics. Baseline was defined as the initiation of treatment. Primary endpoint was liver decompensation (ascites, variceal bleed or encephalopathy), with a follow-up until SVR12. ROC analyses were used to define cut-offs for continuous variables.
Results: 432 patients were included, 318 with Child-Pugh A cirrhosis (CP-A) and 114 Child-Pugh B/C cirrhosis (CP-B/C). Median (IQR) age was 58 (53–63) years and 73 (17%) had genotype 3. 107 (34%) patients with CP-A were treated with PIs and 23 (20%) patients with CP-B/C. SVR was attained in 263 (83%) CP-A patients 86 (75%) CP-B/C patients. Decompensation occurred in 50 (12%) patients, 8 with CP-A and 42 with CP-B/C in a median time of 8 (3–15) weeks. Factors significantly associated with experiencing no decompensation in univariate logistic regression were non-genotype 3 (G3), higher albumin, lower bilirubin, higher ALT, higher platelet (plt) count, lower INR and lower MELD. Among patients without baseline decompensation (no ascites, encephalopathy and normal bilirubin) (n = 266), albumin>38 and platelet count >130 accurately predicted no risk of decompensation. Of patients with baseline albumin>38 and plt count>130, 0 of 68 experienced decompensation. With albumin>38 but plt<130, the risk of decompensation was 3 of 77 (4%) similar to those with albumin<38 and plt>130 (2 of 36 (5.6%)). Of patients with albumin<38 and plt<130, 6 of 85 (7.1%) experienced a decompensation event with treatment. These thresholds were robust in those who received PIs and those who do not.

	Alb<38	Alb>38	Total
Plt<130	6/85 (7.1%)	3/77 (3.9%)	9/162 (5.6%)
Plt>130	2/36 (5.6%)	0/68 (0%)	2/104 (1.9%)
Total	8/121 (6.6%)	3/145 (2.1%)	11/266 (4.1%)

Figure: Risk of decompensation among patients with compensated cirrhosis starting DAA therapy

Conclusion: Patients with cirrhosis who have no evidence of decompensation at baseline and albumin>38 and plt count>130 can safely be treated with DAAs including PI-based therapy with minimal or no risk of decompensation.

THU426
Virological patterns of HCV-patients with failure to second generation direct-acting antivirals

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Background and Aims: Direct-acting antivirals (DAA)-regimens are associated with failure in about 5% of cases. Aim of this work is to characterize the virological patterns and the resistant-associated substitutions (RASs) in the patients(pts) with failure to second-line DAA-regimen. It may help to identify the best approach of new line DAA-regimen.
Method: All the consecutive 63 HCV pts naive with failure to IFN-free regimen observed at the laboratory of infectious diseases of University of Campania, Naples from January 2018 to February 2019 were enrolled. All the pts had been treated with second DAA-regimens (Sofosbuvir+Velpatasvir, Glecaprevir+Pibrentasvir, Grazoprevir/Elbasvir) according HCV genotype, international guidelines and local availability. Sanger sequencing of NS3 (for genotypes 1 and 4), NS5A and NS5B (for all genotypes) was performed at failure by home-made protocols.
Results: Pts enrollerd were mainly males (60%) with median age 67.5 years (range 42–81). HCV RNA, IU/ml median value was 2.27E + 06 (range: 9.08E + 00–1.10E + 07), 33.3% of pts had a diagnosis of cirrhosis. 5 patients were HCV genotype 1a, 41 1b, 5 2a/2c, 9 3a/3 h and 3 were genotype 4. According to therapeutic outcome, 90.5% were relapse, 4.7% were breakthrough and 4.7% were non-response. Among the 63 pts failed at three therapeutic regimens, 19 (30.1%) were been treated with Sofosbuvir + Velpatasvir, 11 (17.4%) with Glecaprevir + Pibrentasvir and 33 (52.4%) with Elbasvir/Grazoprevir. The duration of DAA in months, median (range) 12 (8–24), the timing of resistence test in months at the end of treatment, median (range) 5 (1–19). The NS5A-RASs were more frequent in Sofosbuvir +Velpatasvir (17/19, 89.5%) and in Grazoprevir/Elbasvir (32/33, 97%) failed patients than in Glecaprevir/Pibrentasvir (2/11, 18.2%) failed pts (p = 0,002 and 0,000 respectively). Moreover NS3-RAS were more often detected in pts with failure to Grazoprevir/Elbasvir regimen (10/33, 30.3%) compared to Glecaprevir/Pibrentasvir (1/11, 9.1%) (p = 0,002) and Sofosbuvir + Velpatasvir regimen (2/19, 5.3%) but in this case without statistic significantly. While the NS5B-RAS were infrequent. According to Sofosbuvir + Velpatasvir regimen 36.4% pts showed at least 2 RASs in at least two HCV region including NS5A and 70.3% pts showed at least 2 RASs only in NS5A region. Considering Grazoprevir/Elbasvir regimen 27.3% pts showed at least 2 RASs in at least two HCV region including NS5A and 88% pts showed at least 2 RASs only in NS5A region. (p = 0.00)
Conclusion: Pts can fail also with second-line therapeutic regimens. These pts frequently show mutations above all in the NS5A region, in particular in pts experienced Sofosbuvir/Velpatasvir and in Grazoprevir/Elbasvir regimen than in pts experienced Glecaprevir/Pibrentasvir failure probably due to short lasting of the last cited therapy.

THU427
Global real-world evidence of sofosbuvir/velpatasvir (SOF/VEL) as a highly effective treatment and elimination tool in underserved patient populations experiencing mental health disorders, incarceration or homelessness

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Background and Aims: Successful HCV elimination will require care and cure of difficult to reach populations, including patients with mental health disorders, incarcerated, or homeless. While the WHO guidelines focus on the necessity of engaging these key populations, limited real world effectiveness data (RWD) exist. Simple curative regimens with high sustained virologic response (SVR) rates are key to successful HCV elimination in underserved populations. SOF/VEL is a simple protease inhibitor-free, pangenotypic, panfibrotic, single duration, single tablet regimen, to be taken without regards to food and with limited drug-drug interactions.

This RWD analysis evaluates the effectiveness and tolerability of SOF/VEL for 12 weeks in a worldwide HCV population with mental health disorder, incarcerated or homeless.

Method: 1731 patients from 32 clinical cohorts across Australia, Canada & Europe were managed per local standards of care. Adults were included if SOF/VEL for 12 weeks started before November 2019 and completed while experiencing a mental health disorder, being incarcerated or homeless, irrespective of genotype (GT), presence of compensated cirrhosis (CC) or treatment experience. Exclusion criteria were history of decompensation, prior NS5A-inhibitor exposure, treatment duration >12 weeks or addition of ribavirin. SVR and tolerability were assessed.

Results: Preliminary analysis includes 1143 (71.9% male) patients (51 ± 13.1 years): 691 with a mental health disorder, 341 incarcerated, 111 homeless. 48.9% (559/1143) of patients were taking antipsychotic medication and 55.9% had former or current injecting drug use. 44.6% patients had HCV GT1, 10.9% GT2, 35.0% GT3, 6.7% GT4–6, and 2.8% mixed/unknown GT. 15.5% patients had CC and 13.9% were treatment-experienced.

99.3% (n = 1005/1012) of patients achieved SVR, with SVR between 98.9% and 100% in all 3 priority populations. SVR was 99.6% in non-cirrhotic and 97.5% in CC patients. 131/1143 patients (11.5%) did not have documented SVR, due to non-virological or unknown reason; 95 (72.5%) of whom lost to follow-up. Full analysis will be available at the conference.

Conclusion: SOF/VEL for 12 weeks is a simple, well-tolerated regimen with high cure rates across key patient populations traditionally considered difficult to engage in care across a global context. It allows a test and treat strategy and decentralisation of care, as outlined in the AASLD/ALEH/APASL/EASL joint call to action, enabling reduction of LTFU and implementation of elimination programs.

THU428

Innovative procedures for micro-elimination of HCV infection in a high-risk population of undocumented migrants and low-income refugees

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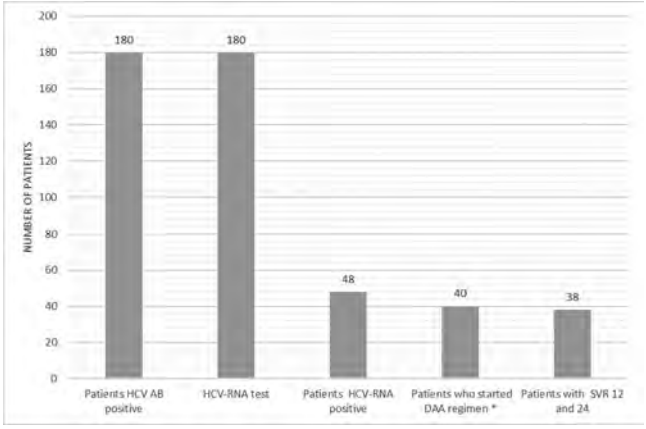
Background: Because of the intermediate HCV endemicity in immigrant populations and of the high efficacy of DAA therapy, programs should be undertaken to eradicate the infection in this difficult-to-manage setting. The aim of the present study was to evaluate an innovative model to eliminate HCV infection in this population, who generally show an anti-HCV positivity rate 3-time higher than that of citizens of the host country.

Method: A prospective, multicenter, collaborative study, based on the active long-term cooperation between five 1st level clinical points and two corresponding 3rd level units of Infectious Diseases (ID) was performed in Campania, southern Italy.

A screening to identify the subjects with HCV infection, free of charge and without bureaucratic procedures, was proposed to all undocumented migrants and low-income refugees prospectively observed by a physician and a cultural mediator at one of the first-level clinical centres from June 2018 to March 2019. All migrants received correct information and illustrated brochures on transmission and prevention of HCV infection, related diseases and available treatments. All anti-HCV positive subjects were addressed at one of the two ID units for further clinical investigation including HCV-RNA determination and, if positive, HCV-genotyping (GT). HCV-RNA positive patients were treated with sofosbuvir plus velpatasvir + ribavirin for 12 weeks and followed up untreated for 12 weeks after treatment withdrawal



Results: Of the 3,401 migrants observed in the study period, 3,286 (96.6%) accepted to be screened. They were young (median age 27 years), predominantly male (83.3%) and came from North Africa (4%), from Sub-Saharan Africa (67.1%), from Eastern Europe (9.3%), from Indo-Pakistan (16.4%) and from other countries (3.2%). Of the

3,286 enrolled subjects, 180 (5.4%) resulted anti-HCV positive. The Figure shows the HCV-cure cascade. All the 180 anti-HCV-positive subjects were linked to care at 3rdIDand tested for HCV RNA and 48 (26.6%) resulted HCV-RNA positive. Of these, 40 (83.3%) started DAA regimen (14 withGT 1b, 21 with 1a, 18 with 3, 4 with 4 and 2 with 2): 38 completed the follow-up with a SVR rate of 100% and 2are still pending. No subject had adverse neither was drop-out.

Conclusion: This innovative procedures for micro-elimination of HCV infection seems to be effective in undocumented migrants and low-income refugees with rates of diagnosis, linkage to care and cure in line with the WHO goals

THU429

Elimination of hepatitis C in a remand prison using a rapid point of care driven test and treat pathway

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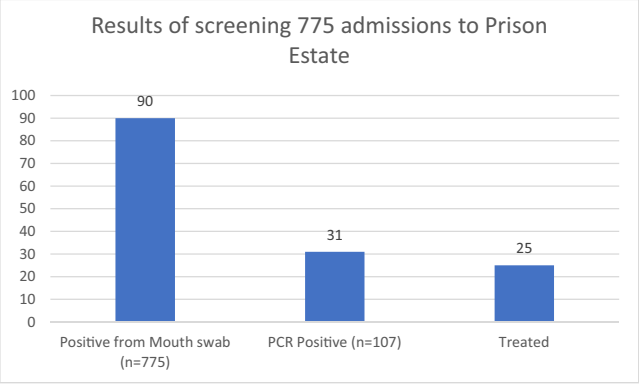
Background and Aims: Micro-elimination in high prevalence settings such as prison estates is seen as an effective strategy for meeting the WHO Hepatitis C elimination targets. We report the successful implementation of a streamlined point of care testing pathway with a rapid treatment strategy that has delivered elimination of hepatitis C in a UK remand prison. The prison has a capacity of 500, receives 45 new admissions week (175/month). Average stay is 6–8 weeks

Method: Individuals were screened on admission with a two-tiered point of care testing strategy. All admissions were first screened for hepatitis C antibodies using a mouth swab (OraSure, OraQuick). Antibody reactive individuals were then tested for hepatitis C PCR using a capillary blood sample (Cepheid, GeneXpert). PCR positive individuals were immediately referred for treatment with a pan-genotypic therapy (Glecaprevir/Pibrentasvir). The strategy was designed to deliver micro-elimination/all prison elimination of hepatitis C, declared when all residents had been tested and all positive residents had started treatment.



Results: The project started on the 8th May. Frontline screening was carried out by HMP nursing staff on secondary health screen (day 2 of arrival). Elimination was declared on 5th September 2019 and has been maintained since. 775 individuals were tested by mouth swab. 90 (12%) patients were hepatitis C reactive. 107 individuals were tested for PCR (17 known to be antibody positive prior to admission). 31 tested positive. 26 started treatment in the prison system. 6 were treated in the community after discharge. 10 (32%) started treatment on the same day that they were diagnosed and 23 (74%) were treated within 8 days. Positive outcomes included reduced stigma, individuals encouraging other residents to be tested, high acceptability of the testing pathway (very few individuals declined the mouth swab screen), provision of a positive health experience and reduction in the burden of the long-term effects of undiagnosed Hepatitis C.

Conclusion: A two-tiered point of care testing strategy with rapid access to treatment using pan-genotypic agents has high acceptability to individuals at risk of hepatitis C, reduced stigma in a prison setting and led to the first ever elimination of hepatitis C in a UK remand prison within 5 months. This test and treat strategy should be tested in other areas of high prevalence where micro-elimination is deemed appropriate.

Submitted on behalf of the All Wales Blood Borne Virus Network

THU430

Dermatological manifestations in the era of new direct acting antivirals: a single-center experience

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Background and Aims: Limited data exist regarding skin disease after introduction of direct acting antivirals (DAAs). When encountering skin lesions in HCV-infected patients treated with DAAs, both HCV related skin manifestations and drug-induced cutaneous adverse effects should be considered. The aim of this study was to analyse possible incidence of dermatological manifestations in patients treated with different DAAs protocols retrospectively.

Method: This case series study included 24 patients (median age 47.5 years) of 9200 patients with chronic HCV recruited from Ain Shams University viral hepatitis and research centre between January 2017 and June 2019. All patients received treatment with DAAs for HCV in conformity with the national protocols. Patients were followed up monthly during the treatment period for liver functions and any clinical complications and three monthly after end-of-treatment. Also, patients were routinely examined during treatment and the follow up period for skin manifestations. All Patients (n = 24) in this study achieved SVR at week 12 and week 24.

Results: Only 24/9200 patients developed dermatologic manifestations. Five of those patients had diabetes mellitus and 15 patients were cirrhotic. Treatment protocols received by affected patients included: Sofosbuvir (SOF) plus Daclatasvir (DAC) (n = 5), SOF plus Simeprevir (SIM) (n = 4) and SOF, DAC and ribavirin (n = 15). Frequency of skin manifestations observed before, during and after DAAs regimen is shown in table (1). All types of lesions showed complete response to standard medical therapies. Conclusion: DAAs can cause different self-limiting dermatologic side effects. Our findings suggest patients treated with DAA may remain at risk for various dermatologic lesions development. Larger prospective studies of patients treated with DAA are needed to better describe the relationship between DAAs and incidence of various skin manifestations, as well as the prognosis of pre-existing lesions after DAA treatment.

Table (1): (abstract: THU430): Frequency of different dermatologic findings in the studied group in different treatment protocols.

Dermatologic manifestation	No of affected patients	Type of treatment								
		Sof/Dac			Sof/Dac/RBV			Sof/Sim		
		Before TTT	During TTT	After TTT	Before TTT	During TTT	After TTT	Before TTT	During TTT	After TTT
Pruritus	6	0	1	1	0	1	1	0	2	0
Eczema	2	0	1	0	0	0	1	0	0	0
Bullous eruption	1	0	0	0	0	0	0	0	1	0
Urticarial	3	0	0	2	0	1	0	0	0	0
Gen. Polymorphic Eruption	4	0	0	0	0	1	2	0	0	1
Erythema nodosum	1	0	0	0	0	0	1	0	0	0
Lichen planus	2	0	0	0	0	0	2	0	0	0
Photosensitivity	1	0	0	0	0	1	0	0	0	0
Actinic keratosis	1	0	0	0	0	0	1	0	0	0
vitiligo	1	0	0	0	0	0	1	0	0	0
Alopecia	1	0	0	0	0	1	0	0	0	0
Hyperhidrosis	1	0	0	0	0	0	1	0	0	0
Total No.	24	5			15				4	

THU431

Hepatitis C treatment outcomes among people who inject drugs accessing harm reduction services in Kenya

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Background and Aims: Sub-Saharan Africa has among the highest global hepatitis C virus (HCV) prevalence. To meet the WHO's goals for HCV elimination, treatment is needed as part of a comprehensive strategy; however, access to direct-acting antiviral (DAA) therapy has been limited in many low- and middle-income countries (LMICs). HCV treatment among people who inject drugs (PWID) is of particular importance to prevent forward transmission of HCV. Since PWID are a hard to reach population, medication-assisted treatment (MAT) and needle syringe programs (NSP) are potential access points where HCV treatment can be delivered. However, little is known about the feasibility and effectiveness of HCV treatment among PWID in LMICs in MAT and NSP settings.
Method: This study was part of a supplement to the Testing and Linkage to Care for Injection Drug Users (TLC-IDU) Kenya study. The TLC-IDU study was a stepped wedge cluster-randomized trial evaluating the effectiveness of a "seek, test, treat, and retain" approach to HIV community viral load suppression among PWID accessing NSP service sites in Nairobi, Coastal and Western Kenya. Participants from the TLC-IDU study were screened with rapid HCV antibody tests. Those who were antibody-positive were confirmed with HCV RNA tests and genotyped if viremic. We offered DAAs under directly observed therapy (DOT) to 95 participants. All participants had clinical exams and AST to platelet ratio (APRI) scores prior to treatment with sofosbuvir/ledipasvir. The primary endpoint was the proportion of participants with a sustained virological response 12 weeks after therapy (SVR12).
Results: Of the 95 participants who were offered HCV treatment for this sub-study, 51 were genotype 1a, 41 were genotype 4a, and 3 were genotype 1a/4a. Twelve were cirrhotic, 65 were treated in MAT, and 30 were treated in NSP. Of 95 participants, 5 (5.3%) were lost to follow-up after initiating treatment (2 from MAT, 3 from NSP). The other 90 (94.7%) participants were retained. Of those who were retained, 82/90 (91.1%) achieved SVR12–82/95 (86.3%) overall. Two participants had undetectable HCV RNA at the end of treatment (EOT), but were detectable 12 weeks following treatment; SVR12 results were unknown for 3 participants (2 refused blood draw, and the assay could not be performed for 1); 2 discontinued treatment; 1 died before EOT.
Conclusion: HCV treatment in MAT and NSP sites appears to be feasible with high SVR12 rates. These results need to be interpreted with caution given those who were most interested were retained for HCV treatment in this sub-study. Additional studies will be required to assess optimal models of care for HCV treatment among PWID in LMICs given DOT may be infeasible when resources are not sufficient. Additionally, reinfection following successful HCV treatment will need to be evaluated.

THU432

Real-life experience of direct acting antiviral treatment for chronic hepatitis C infection in adolescent patients in a low prevalence setting

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Background and Aims: The global prevalence of hepatitis C virus infection (HCV) is estimated to be 177 million people (2.5%). Chronic HCV infection is associated with cirrhosis and hepatocellular carcinoma. Direct acting antivirals (DAT) for HCV have been licensed for use in adults since 2011 and have a cure rate of >95%. In 2018 the European Society of Paediatric Gastroenterology, Hepatology And Nutrition gave guidance on the use of DAT in children >12 years of age and >35 kg in weight. Currently 2 DATs are licensed to treat HCV in adolescents including; a 12 week course of Ledipasvir/Sofosbuvir and an 8 week course of Glecaprevir/Pibrentasvir.
Method: All children with chronic HCV in Ireland are treated in the rainbow paediatric infectious disease clinic. In 2017, the National HCV Treatment Programme agreed to extend access to DAT to our

paediatric cohort. The aim of our study was to evaluate DAT in our paediatric cohort.
Results: 31 adolescents have been eligible for DAT in our service, of which 26 (84%) have commenced and completed DAT, 3 patients were lost to follow up and 2 patients have deferred treatment until next summer. All patients completed therapy, no patient reported serious adverse drug reactions and 7 patients reported adherence issues. Median age at commencing DAT was 15.6 years (range 12.9–19.6years). 12 patients (46%) lived with their biological parent/s, a further 35% lived with extended family members and 19% were in foster/residential care. All patients with HCV genotype 1 received Ledipasvir/Sofosbuvir (n = 24), whilst the remaining 2 patients with genotype 3 received Glecaprevir/Pibrentasvir. Median pre-treatment HCV Viral Load (VL) was Log 5.87 (range Log 4.27–7). 23 of 26 patients had undetectable VL at treatment end, 2 had a VL below the limit of detection and 1 failed to attend for testing. 20 patients achieved a SVR 3 months from end of treatment, 5 have SVR results pending and 1 patient was lost to follow up.
Conclusion: Our study reaffirms the successful cure rate with DAT for adolescents with chronic HCV. Challenges with DAT in our patient cohort included; 1) adherence with treatment protocol 2) complex social backgrounds and 3) coordination of DAT monitoring with educational examinations. To ensure optimal success of DAT in a non clinical trial setting we suggest careful patient selection, advanced patient preparation, ongoing patient follow up and parental/guardian support from a multidisciplinary team.

THU433

Treatment of hepatitis C at the Stockholm needle syringe program - treatment success, reinfection rates and challenges for HCV elimination

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Background and Aims: The Stockholm Needle Syringe Program (NSP) has since the start in 2013 enrolled over 3,500 participants. Annually, around 1,800 persons make 26,000 visits at the Stockholm NEP. 43% inject mainly heroin and 43% amphetamine. Mean age is 39 years and mean duration of injection drug use is 18 years. 21% are homeless. The viremic HCV prevalence is 55%. Although injection risk behaviors decrease significantly over time among participants, HCV incidence remains high with an incidence rate of 22/100 person years.
Method: Since January 1st 2018, participants at the Stockholm NSP are HCV treated without reimbursement restrictions. Patients were HCV RNA tested at EOT, SVR12 and every 6 months post SVR.
Results: So far 124 participants (>75% amphetamine users) have initiated HCV treatment. 100/114 (88%) were HCV RNA negative at end of treatment (EOT), 10 participants dropped out 1–2 weeks after treatment initiation and two after 6–7 weeks. Another two participants were lost to follow-up. Thus, all participants who completed treatment, with a follow-up HCV test (n = 100), were HCV RNA negative at EOT. Overall, 73/95 (77%) reached SVR12 (12 drop-outs and 10 lost to follow-up). All with a follow-up test at SVR12 + (n = 73) were HCV RNA negative. 5 reinfections post-SVR occurred, corresponding to a reinfection rate of 10.6/100 PY. One reinfection was spontaneously cleared, leaving a persistent reinfection rate of 8.5/100 PY. On a parallel level, there were 146 new HCV infections

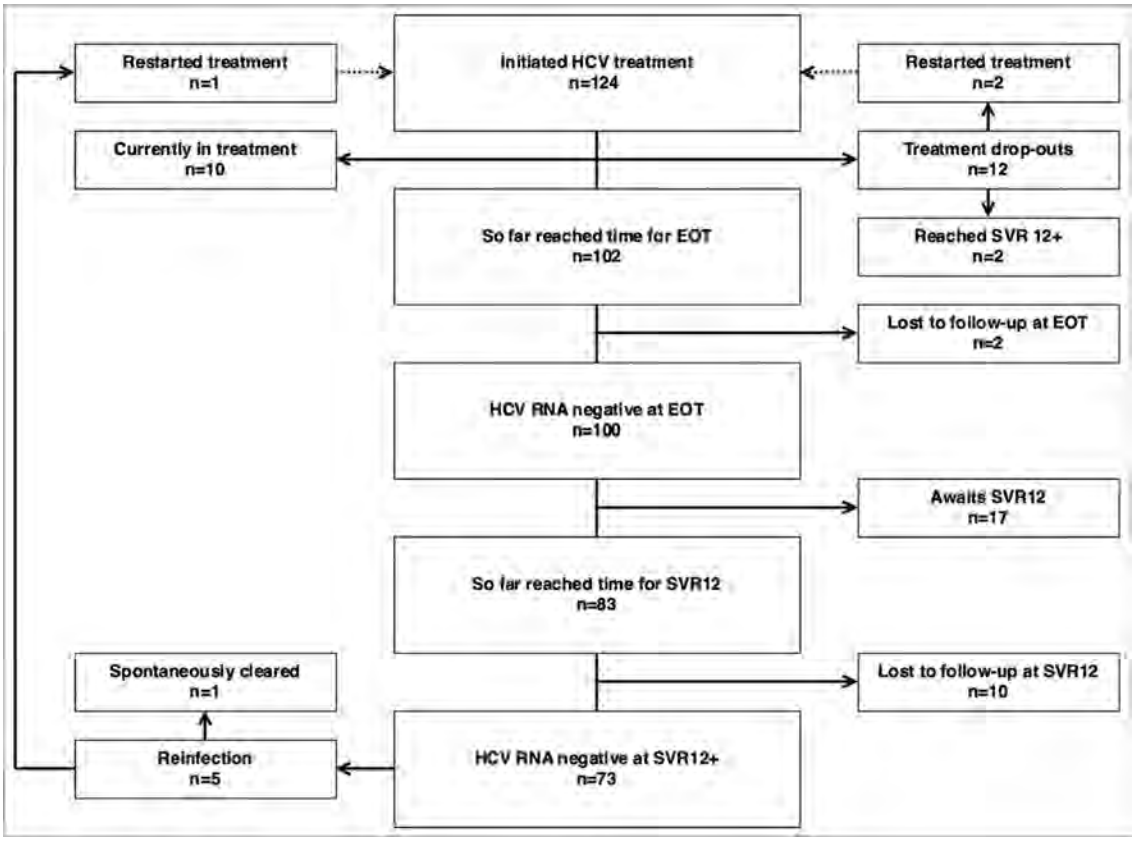

Fig 1: (abstract: THU433): Flowchart of HCV treated patient at the Stockholm Needle Syringe Program. "SVR 12+" refers to an SVR test at week 12 or later.

(seroconversions/reinfections) in the non-treated cohort during the study period.
Conclusion: Even though 8–10% of the HCV viremic patients were treated annually at the Stockholm NSP, the number of new HCV infections were higher than the total number treated. A high prevalence of HCV and amphetamine use (not eligible for effective substance use disorder treatment) thus constitutes a great challenge for HCV elimination.
Further treatment data and reinfection data is pending and will be presented at ILC 2020.

THU434
Epidemiological and clinical analysis of foreign patients treated with direct antivirals for hepatitis C in a high immigration area

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Background and Aims: Although Spain has a low prevalence for hepatitis C (HCV) (0.85% seropositivity and 0.22% active infection), in the immigrant population this seroprevalence is estimated at 1.3–1.6%, with important differences according to origin. Our aims were to analyze the epidemiological and clinical characteristics of immigrants treated since the appearance of direct-acting antivirals (DAA) for HCV in our geographic area, and their possible differential features.
Method: Descriptive cross-sectional study on all HCV monoinfected immigrant patients treated with DAA (without Interferon) in two hospitals. Medical records and epidemiological data collected in Primary Care were reviewed.
Results: 149 immigrant patients were treated (89 Poniente, 60 Torrecárdenas), out of a total of 1314 treatments (11.3% from total). They came from 27 different nationalities, mostly from Eastern Europe and former USSR (EEu 55.4%), Sub-Saharan Africa (SubS 18.9%) and Maghreb (Mgb 15.5%). They presented an average of 12.6 +/– 8.2 years in Spain, being the EEu and Mgb who showed a greater median stay (14–16 years vs 9–10 years in other origins, $p = 0.035$). The viral load expressed in Log10 was 5.74 +/– 0.94, ALT 63.43 +/– 54.83 U/L and platelets 201 +/– 69 × 109/L. Most of them had absent or minimal fibrosis (54.1%). The genotypic distribution was the only infection-related variable that showed differences according to origin ($p < 0.001$), since the SubS had 84.0% of G2-G3, compared to a predominance of G1 in the rest. There are no SVR12 data from 24 patients (6 losses, 18 pending SVR). The overall SVR of the remaining 125 was 95.7% with 4 incidences of adherence: 2 dropouts, 1 dose failure (1 pill t.i.d. instead of 3 pills together daily, no SVR) and a suspension due to error (resumed after 2 weeks and obtained SVR).
Conclusion: The majority of immigrants treated with DAA in our health area come from Eastern Europe, have low fibrosis and only show differences in their genotypic distribution according to origin. The SVR12 is similar to that recorded in real-life cohorts, with little impact on therapeutic adherence.

THU435
Drug-drug interactions (DDIs) with pangenotypic direct-acting antivirals (DAAs) in patients with hepatitis C; understanding the populations at risk and real-world care management

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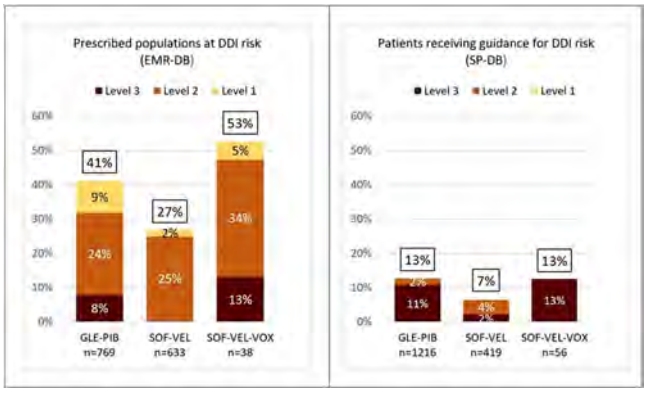
Background and Aims: Several studies have assessed the frequency and nature of DDIs with DAAs, but few have assessed care management for identified DDIs. We used two complementary data sources to initially identify DDI risk for DAAs and a second source to describe healthcare providers actions in care of HCV patients with potential DDIs.
Method: To assess DDI risk, data for patients prescribed DAAs in 2018 were collected from a propriety US EMR database (EMR-DB) covering 21 healthcare organizations and 26MM patients and possible interacting drugs identified. Per the Hepatitis Drug Interaction Database from The University of Liverpool, DDIs were considered potential weak interaction (level 1), potential interaction (level 2), or contraindicated (level 3). Real-world recommendations and resultant actions regarding DDIs were obtained from a specialty pharmacy database (SP-DB) and were specific for patients prescribed glecaprevir-pibrentasvir (GLE-PIB), sofosbuvir-velpatasvir (SOF-VEL), or SOF-VEL-voxilaprevir (SOF-VEL-VOX).
Results: The EMR-DB study population consisted of 2214 DAA-prescribed HCV patients of which 35% (769) were prescribed GLE-PIB, 29% (633) SOF-VEL, and 2% (38) SOF-VEL-VOX. Potential DDIs were identified in 41% (317/769) GLE-PIB prescribed patients, 27% (170/633) SOF-VEL, and 53% (20/38) SOF-VEL-VOX. [Figure] Top DDI drug classes for GLE-PIB were level 2 analgesics (139/317, 44%); for SOF-VEL were level 2 PPIs (83/170, 49%); and for SOF-VEL-VOX were level 2 PPIs (6/20, 30%). The SP-DB study population consisted of 1691 HCV patients. Potential DDIs that resulted in guidance to the physician were observed in 12% (151/1216) GLE-PIB prescribed patients, 7% (28/419) SOF-VEL, and 13% (7/56) SOF-VEL-VOX. [Figure] Recommendations varied by DDI, patient, and disease characteristics and consisted of "hold interacting drug," "modify dose of interacting drug," "switch interacting drug," or "proceed but monitor." The recommended guidance was not followed for 10% (15/155) GLE-PIB prescribed patients, 36% (10/28) SOF-VEL, and 43% (3/7) SOF-VEL-VOX.

Variable		EastEurope (n=82)	SubSahara (n=28)	Mgb/MEast (n=23)	Others (n=15)	p
Age		43,6 (36,8-51,0)	46,5 (31,2-52,5)	50,0 (45,0-59,0)	53,3 (44,0-57,0)	p=0,003
Time in Spain (years)		14,0 (11,0-16,0)	9,0 (2,2-13,7)	16,0 (10,0-20,0)	10,0 (4,0-14,0)	p=0,035
Viral load log10		5,68 (5,07-6,35)	5,94 (5,01-6,80)	5,74 (5,54-6,30)	6,03 (5,68-6,67)	ns
Genotype n(%)	1	58 (76,3%)	4 (16,0%)	14 (63,6%)	10 (66,7%)	p<0,001
	2-3	18 (23,7%)	21 (84,0%)	8 (36,4%)	5 (33,3%)	
Fibrosis n(%)	F0-F1	46 (57,5%)	17 (63,0%)	11 (50,0%)	6 (42,9%)	ns
	F2-4	34 (42,5%)	10 (37,0%)	11 (50,0%)	8 (57,1%)	
Platelets <150x10^9/L n(%)		19 (23,5%)	4 (14,3%)	7 (30,4%)	7 (46,7%)	ns
ALT≥35U/L n(%)		54 (66,7%)	19 (67,9%)	12 (52,2%)	13 (86,7%)	ns

Figure: (abstract: THU434)



Conclusion: Prevalence of DDI is very common for HCV treatment and more frequent in protease-containing regimens and associated with common medications. Recommendations for identified DDIs in real-world care are given for level 2 and 3 DDIs and physician response is highly variable.

THU436

Patient-reported outcomes among people receiving opioid agonist therapy and treatment for hepatitis C virus infection: results from CO-STAR

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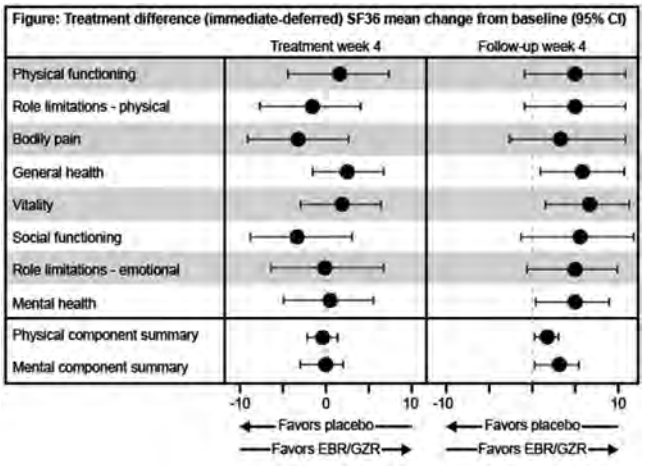
Background and Aims: The CO-STAR study evaluated the safety and efficacy of elbasvir/grazoprevir (EBR/GZR) administered for 12 weeks in participants with hepatitis C virus (HCV) infection receiving opioid agonist therapy (OAT). Sustained virologic response was achieved by 96% of participants. The aim of this analysis was to evaluate changes in health-related quality of life (HRQOL) in the study population.
Method: Participants on OAT were randomized to receive the fixed-dose combination of EBR/GZR (50 mg/100 mg daily) or placebo once daily for 12 weeks. Participants remained blinded until follow-up week (FW) 4, after which those randomized to placebo initiated deferred treatment with EBR/GZR. HRQOL was measured at baseline, treatment week (TW) 4, end of treatment (EOT), and FW4 before any study-related procedures using the Short Form-36v2 survey. Difference in mean change from baseline scores >5% for individual domains or >2%–3% for physical/mental component summary (PCS/MCS) scores were considered clinically meaningful.
Results: Participants were primarily white (80%) and male (76%) with HCV genotype 1a infection (76%); 59% had a positive urine drug screen at baseline. At baseline, mean MCS and PCS scores for EBR/GZR (n = 198) and placebo (n = 98) treatment groups were 44.4 (standard deviation [SD] 11.4) vs 43.4 (SD 11.6) and 48.6 (SD 8.7) vs 49.1 (SD 9.6), respectively. At TW 4 and EOT, the differences in mean change from baseline MCS and PCS scores (EBR/GZR – placebo) suggested no clinically meaningful difference between EBR/GZR and placebo. The difference in mean change from baseline at FW4 in general health (6.0%; 95% CI 1.4–10.6), vitality (6.8%; 95% CI 1.9–11.8), and mental health (5.2%; 95% CI 0.5–9.8) domains suggests clinically meaningful improvements in participants receiving EBR/GZR compared with those receiving placebo (Figure). The difference in mean change from baseline scores (EBR/GZR – placebo) for the MCS was also considered clinically meaningful (2.8%, 95% CI 0.3–5.4). Significant differences at FW4 were not observed in physical functioning, role limitations (physical), bodily pain, or the PCS.



Conclusion: Post-treatment improvement in HRQOL was observed in participants on OAT receiving EBR/GZR compared with those receiving placebo. Clinically meaningful improvements were noted in the general health, vitality, and mental health domains. Improvement in general and mental health adds to the benefits of HCV therapy among people who inject drugs.

THU437

Real-world effectiveness of sofosbuvir/velpatasvir/voxilaprevir as a hepatitis C virus infection salvage treatment

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Background and Aims: First-line direct acting antiviral agents (DAAs) are highly effective (90%–95%), yet some hepatitis C (HCV) patients do not achieve sustained virologic response (SVR). In patients previously treated with DAAs, sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) has shown high SVR rates in clinical trials. We assessed the effectiveness of SOF/VEL/VOX in treating treatment-experienced patients with HCV genotype 1 (GT1) to genotype 6 (GT6) infection in a large population-based Canadian cohort.
Method: This analysis included individuals in the British Columbia (BC) Hepatitis Testers Cohort who had virological failure after prior DAA therapy, initiated SOF/VEL/VOX for retreatment of GT1-GT6 on or prior to June 30, 2019, and had at least one HCV RNA test after treatment initiation. SVR was assessed from treatment start until Oct 9, 2019. The primary outcome was SVR at 12 weeks following end of HCV treatment based on modified intention-to-treat, where

individuals with a negative HCV RNA test after treatment end but no SVR assessment were excluded.
Results: Overall, 191 people treated with SOF/VEL/VOX (n = 153) or SOF/VEL/VOX+ribavirin (RBV; n = 38) were included in the analysis. The majority of were infected with GT1 (n = 104, 54.5%) or GT3 (n = 62, 32.5%), followed by GT2 (n = 17, 8.9%). Most individuals were male (82.2%) and aged ≥ 50 years (92.1%). The largest proportion of patients received SOF/ledipasvir (SOF/LDV; 37.2%), followed by SOF/VEL (14.1%) and SOF+RBV (13.6%) and as their last treatment. The overall SVR rate with SOF/VEL/VOX salvage treatment was 95.3% (182/191). SVR for GT1, GT2 and GT3 was 96.2%, 100%, and 91.9%, respectively. SVR was lower (but not statistically significant) for those with cirrhosis vs. no cirrhosis – overall (88.0% vs 96.4%) and across previous treatment regimens: SOF/VEL (75.0% vs 91.3%), SOF/LDV (85.7% vs 96.5%), SOF-containing (87.0% vs. 96.2%) and NS5A + SOF (84.2% vs. 95.1%).

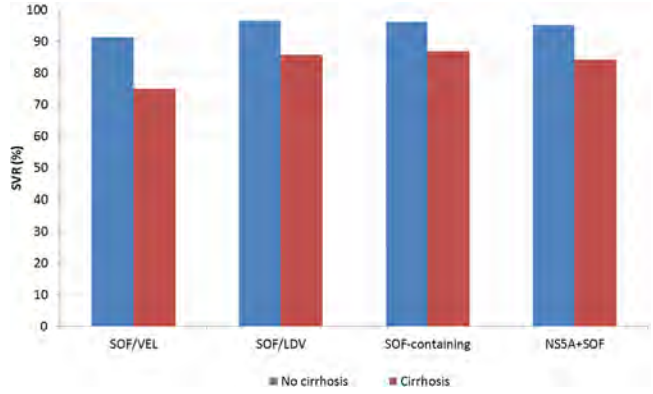

Figure: SVR among patients treated with SOF/VEL/VOX by cirrhosis status and previous treatment regimen

Conclusion: In this real-world cohort of patients with virological failure after prior DAA therapy, retreatment with SOF/VEL/VOX resulted in SVR rates of more than 90% across all genotypes; however, SVR was lower for those with underlying cirrhosis. Comparisons were limited by small sample sizes.

THU438

A combination of AT-527, a pan-genotypic guanosine nucleotide prodrug, and daclatasvir was well-tolerated and effective in HCV-infected subjects

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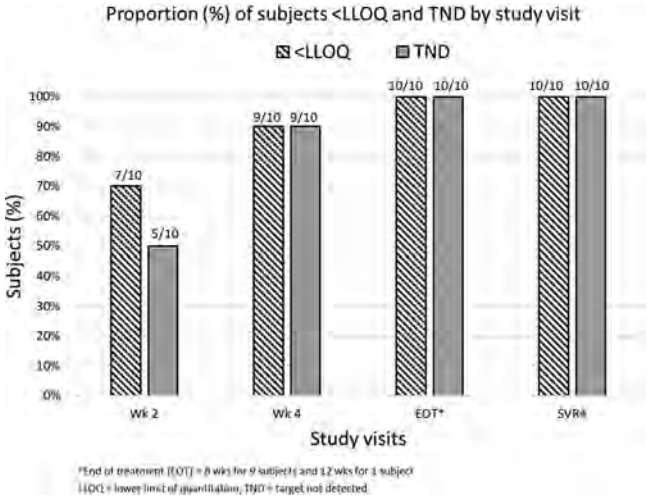
Background and Aims: AT-527 is a novel modified guanosine nucleotide prodrug inhibitor of the hepatitis C virus (HCV) NS5B polymerase, with a highly differentiated profile compared to sofosbuvir. AT-527 exhibited profound pan-genotypic antiviral activity after 550 mg once daily (QD) dosing for 7 days in HCV-infected patients with or without cirrhosis. The current pilot phase 2 study was conducted to evaluate the long-term safety, viral kinetics and efficacy of AT-527 in combination with daclatasvir, the only approved stand-alone NS5A inhibitor.
Method: A cohort of 10 treatment-naïve, genotype (GT) 1-infected subjects without cirrhosis received 550 mg AT-527 and 60 mg daclatasvir QD. The protocol allowed subjects who achieved HCV RNA < lower limit of quantitation (LLOQ) by wk 4 to stop treatment after 8 wks. Otherwise, subjects were to receive 12 wks of treatment. Safety assessments included adverse events (AEs), vital signs, electrocardiograms (ECGs) and standard safety laboratory tests. Viral kinetics were evaluated by monitoring plasma HCV RNA using the Roche Cobas® quantitative test on the Cobas® 6800/8800 system (LLOQ = 15 IU/mL).
Results: The 10 enrolled subjects (5 African origin and 5 European origin) had the following demographic characteristics: mean age 39 yrs (range: 26–57), 8 male/2 female, mean HCV RNA 6.8 $\log_{10}$ IU/mL (range: 6.0–7.5), 6 GT1a/4 GT1b, mean ALT 72 U/L (range: 22–181). All subjects (100%; 10/10) achieved SVR4. Nine subjects received 8 wks of treatment, and one subject received 12 wks of treatment. The study drugs were well tolerated with no discontinuations or serious AEs. AEs were generally mild and transient. ALT decreased rapidly with dosing and normalized by wk 2. There were no clinically significant changes in vital signs or ECGs. Viral load declined rapidly with 7/10 (70%) subjects achieving HCV RNA < LLOQ by wk 2 (5 had non-detectable HCV RNA at wk 2). SVR12 data will be presented at the meeting.



Conclusion: AT-527 in combination with an HCV NS5A inhibitor (daclatasvir) was well-tolerated and highly effective. All subjects achieved SVR4. Very rapid early clearance of HCV RNA supports continued evaluation of AT-527 in short treatment regimens of 8 wks or less.

THU439

Frequency and characteristics of DAAs failure in hepatitis C therapy

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Background and Aims: Since the introduction of DAAs there have been advances in its effectiveness and changes in the characteristics of treated patients. To know the evolution in the rate of therapeutic failures (TF) and their characteristics in a series of patients with hepatitis C treated with DAAs without IFN.
Method: 1149 patients treated with DAAs between Jul/14 and Mar/19 divided into 2 time periods (PI: Jul/14–Jun/17; n = 755 and P-II: Jul/17–Mar/19; n = 394) were analyzed. TF were classified as virological (V) and non-virological (NV). Discontinuation of treatment for any reason that led to a lack of SVR, death between the end of the treatment and +12 weeks control, as well as no attendance to that control were classified as NV.

Results: Globally TF was observed in 53/1149 (4.6%) patients [36/755 (4.7%) in P-I and 17/394 (4.3%) in P-II; p = 0.72]. Compared to P-I, P-II patients were younger [53.0 (46.7–59.6) vs. 55.1 (49.9–64.0) p < 0.001], most often immigrants (7.8% vs. 3.9%; p = 0.001), with more frequent history of PWID (48.5% vs. 36%; p < 0.001), anti-psychotic treatment (11.4% vs. 7.5%; p = 0.029), GT-3 infection (21% vs. 11.9%; p < 0.001) and naive (75% vs. 63%; p < 0.001). In contrast, the proportion of patients with cirrhosis was higher in P-I (46.6% vs. 14.4%; p < 0.001). 56% of P-II patients versus 4.5% of P-I received pangenotypic DAAs (p < 0.001). There were no differences between the two groups in sex (p = 0.35), treatment with methadone (p = 0.098) or anti-depressants (p = 0.31) or excessive alcohol consumption (p = 0.15). Of the 36 TF of P-I, 23 (63.8%) were V, while 16/17 (94.2%) that occurred in P-II were NV (p < 0.001). The most frequent cause of NV failure in P-II was the non attendance to the control in week +12 without apparent cause (12/16; 75%). In the univariate, NV failure was associated with age ≤ 55 years (p < 0.001), methadone treatment (p < 0.001), immigration (p = 0.004), history of PWID (p = 0.042) and treatment on P-II (p = 0.016); in the multivariate only methadone treatment (OR: 5,069; 95% CI: 2,338–10,989; p < 0.001) and being an immigrant (OR: 5,536; 95% CI: 1,946–15,774; p = 0.001) were associated with NV failure.

Conclusion: Despite the better profile of patients and drugs, the rate of TF remains stable along the study period. However, the type of failure has changed, being the NV the most important one since 2017. It is necessary to make an effort aimed at improving patients adherence to treatment and clinical visits, especially in immigrants and those on methadone treatment.

THU440

Real-world clinical practice outcomes in hepatitis C-infected patients with psychiatric and substance use disorders treated with glecaprevir/pibrentasvir for 8 or 12 weeks: a pooled analysis across nine countries

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Background and Aims: Barriers to treatment with DAAs still exist in patients with dual pathologies (ie, psychiatric and substance abuse disorders). Real world data are critical to inform clinical decisions and achieve WHO elimination targets. Glecaprevir/pibrentasvir (G/P) is approved for treatment of chronic hepatitis C virus (HCV) genotypes 1–6. In treatment-naïve patients, G/P was recently approved for shorter treatment duration (8 weeks) in patients with or without cirrhosis. We evaluated real-world effectiveness, safety, and patient-reported outcomes (PROs) of G/P in marginalized HCV-infected patients in ongoing post-marketing observational studies.

Method: Data were pooled from Austria, Belgium, France, Greece, Israel, Italy, Poland, Portugal, and Switzerland (13 Nov 2017–02 Oct 2019). Treatment naïve or experienced patients aged ≥ 18 years with or without cirrhosis were included. Patients received G/P consistent with local label and/or at treating physician's discretion (1608 [84%] received G/P for 8 weeks). Percentage of patients in the core population with sufficient follow up (CPSFU) who achieved sustained virologic response at post-treatment Week 12 (SVR12) was assessed overall and for each subgroup. The mean (SD) change in PROs (36-Item Short Form Health Survey [SF-36] mental [MCS] and physical component summary [PCS] scores) from baseline to SVR12 visit was reported (minimally important difference ≥ 2.5). Safety was assessed in patients receiving ≥ 1 dose of G/P.

Results: Of 1922 patients receiving ≥ 1 dose of G/P, 640 (34%) had used illicit substances, 184 (10%) had psychiatric disorders, 300 (18%) had a history of alcohol use, and 768 (44%) were unemployed or had low to no education. In the CPSFU population, the SVR12 rate was 98.4% (1510/1535) overall, 98.3% (1332/1355) in treatment-naïve patients, 98.9% (175/177) in treatment-experienced patients, and

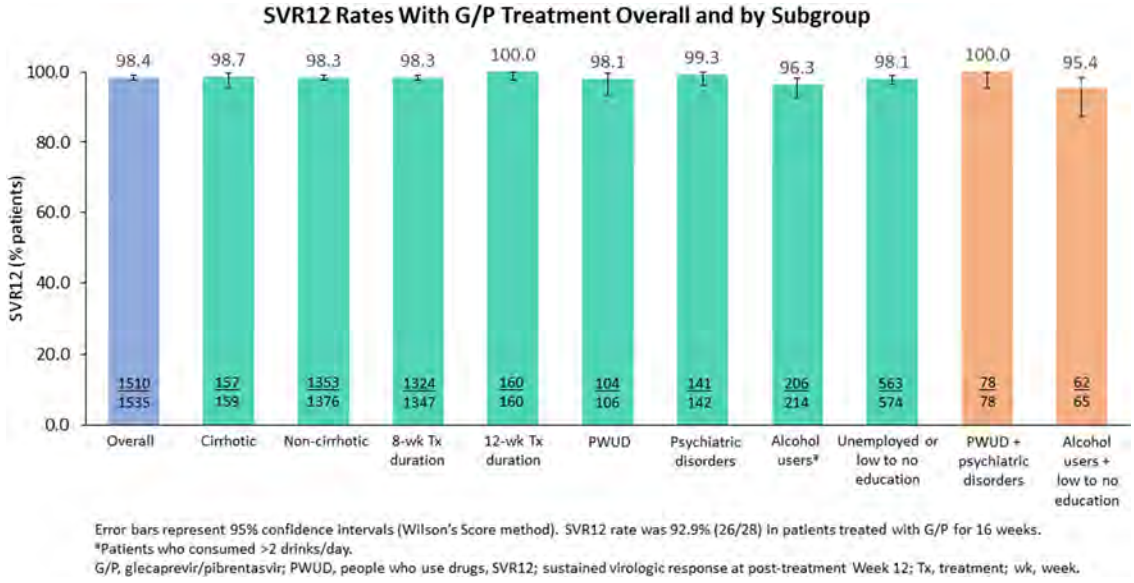

Figure: (abstract: THU440)

high (>95%) across all subgroups (Figure). Overall, mean change from baseline in MCS and PCS was 3.4 (10.5) and 2.1 (7.9), respectively, at SVR12 visit. In the total population (N = 1922), 1 G/P-related serious adverse event (pericarditis) was reported; 6 patients (0.3%) discontinued G/P due to drug-related adverse events. The most common adverse events were asthenia (2.2%), fatigue (2.0%), and headache (2.0%).

Conclusion: The 8- or 12-week G/P regimen was highly effective and well tolerated in marginalized patients with single or dual pathologies infected with chronic HCV in the real world.

THU441

Fast-track-consultation protocol: an interdisciplinary and useful tool for treating drug user hepatitis C infection in addiction out-patient units

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Background and Aims: Hepatitis C (HCV) infection treatment in high-risk of transmission patients (e.g. persons who injected drugs) should be a priority. However, adherence to direct acting antiviral therapy (DAA) may be low in this population. The aim of this study is to analyze the results of using a fast-track-consultation protocol in terms of adherence and response to HCV treatment in addiction out-patient units.

Method: A prospective observational study has been conducted. Addiction out-patient units' users with positive HCV-RNA by dried blood spot (DBS) were included from March to September 2019.

A specific protocol was used. The patients included were referred to fast-track-consultation with the help of addiction units' workers. In a sole appointment, all patients were seen by an hepatologist, a complete analysis and a liver fibrosis assessment by transient elastography were performed and finally, treatment was started. Addiction units' workers supervised and encouraged patients during the treatment. They also provided DBS at the end of the treatment and twelve weeks after treatment cessation. If a patient lose follow-up, the hepatologist sent an encrypted email to addiction unit´s workers to localized and gave him a new appointment.

Results: One-hundred and two patients were included in this analysis (9 women; mean age 49.3 years [SD = 7.0]). Most of the patients (45.1%) presented genotype 1 HCV and 91.2% were naïve to treatment. Seventeen patients (16.7%) suffered from mental disorder diagnosed by a psychiatrist and 16 had an unstable housing during treatment. Almost all patients (97.1%), received Sofosbuvir-Velpatasvir.

By this moment, sixty-nine patients have completed the treatment plan and 26 have the treatment ongoing. The HVC-RNA from 64/69 patients (92.8%) at the end of the treatment and 18/20 patients (90%) at twelve weeks post-treatment is available. They were all negative.

Seven patients (6.9%) did not finish the first DAA treatment. Most of them (6 patients) lose follow-up, but four of them, thanks to the protocol, were rescued and finally completed the treatment.

Conclusion: The interdisciplinary fast-track-consultation protocol is a useful method to achieve high rates of treatment adherence and sustained viral response in HCV patients from addiction out-patient units.

THU442

Achieving hepatitis C elimination in people who inject drugs - interim results of an innovative screen-and-treat program in Austria

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Background and Aims: To achieve the WHO goal of hepatitis C virus (HCV) elimination by 2030, strategic and tailored screening and treatment projects are essential. In Austria, people who inject drugs (PWIDs) represent the most important high-prevalence population. In Vienna there are about 6.500 PWIDs on opioid substitution therapy (OST). Our aim was to eliminate HCV in this population by a combined screen-and-treat strategy.

Method: Study part 1: According to our experience a considerable subgroup of PWIDs with HCV are reluctant to attend tertiary care centers who provide direct-acting antiviral (DAA) therapy. Next to poor adherence, they are unlikely to maintain a regular drug intake if provided with DAAs for self-administration at home. Therefore, HCV treatment was performed as "directly observed therapy" (DOT) since the end of 2014: Patients received DAA together with OST under direct supervision of medical staff at a pharmacy or a low-threshold facility.

Study part 2: In Vienna, every PWIDs on OST has to renew their long-term OST at one of the nine health authority centers once a month – rendering these health authority centers as an ideal interface for HCV screening. In our project all PWIDs are offered saliva-based testing for anti-HCV antibodies (OraQuick®) - followed by HCV-RNA PCR in case of a positive anti-HCV result. HCV-RNA(+) PWIDs are then referred to a low-threshold facility for initiation of DAA therapy.

Results: Study part 1: Using the concept of DOT, only 0.3% of scheduled dates for DAA intake together with OST were missed by the n = 409 included patients. So far, 289 of 290 (99.7%) PWIDs who finished treatment and 12 weeks of follow-up have achieved SVR12; one patient with genotype 3 HCV infection showed nonresponse. Reinfection was recorded in 18/289 (6.2%) patients. 89/409 (21.8%) patients are still on treatment and n = 30/409 (7.3%) were lost to follow-up.

Study part 2: Screening at health authority centers was well accepted by PWIDs. So far, 2810 patients were included: 34.6% of patients already knew about their HCV-status and were sent to the low-threshold facility for further evaluation and treatment. Of the tested population 46.5% showed anti-HCV(+), of whom 34.4% were viremic.

Conclusion: The concept of DOT is highly effective in PWIDs on OST with a high risk of non-adherence to DAA therapy. HCV-screening of PWIDs at public institutions is well accepted and has the potential to identify a considerable number of unknown HCV cases.

THU443

Directly observed therapy for hepatitis C with sofosbuvir/velpatasvir alongside opioid substitution as a tailored microelimination strategy in PWIDs with a high risk of non-adherence - real-world data from Vienna, Austria

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Background and Aims: Directly acting antivirals (DAA) against hepatitis C virus (HCV) infection have facilitated sustained virologic response (SVR) rates >90% in clinical studies. Yet, real life data regarding DAA treatment in people who inject drugs (PWIDs) are scarce. We evaluated the effectiveness of sofosbuvir/velpatasvir (SOF/VEL) in difficult-to-treat PWIDs with a presumed high risk for non-adherence to antiviral therapy using an innovative concept involving their opioid substitution therapy (OST) facility.
Method: N = 250 patients (m/f: 186/64; median age: 45.1 years (IQR 16.9); HCV-genotype (GT) 1/2/3/4/unknown: 119/5/109/10/7, GT3: 43.6%; cirrhosis: n = 88; 35.2%) treated with SOF/VEL were included. PWIDs at high risk for non-adherence to DAA therapy (n = 145) received HCV treatment alongside their OST under the supervision of medical staff ("directly observed therapy", DOT). The effectiveness of SOF/VEL given as DOT in PWIDs with presumed high risk for non-adherence to antiviral therapy was compared to patients with presumed "excellent compliance" in the "standard setting" (SS) of SOF/VEL prescription at a tertiary care center and self-managed SOF/VEL intake at home (n = 105). Treatment duration was 12 weeks according to the SOF/VEL drug label.
Results: DOT-patients (n = 145/250; 58.0%) were younger than SS-patients (median age: 41.6 years (IQR 12.3) vs. 53.8 years (IQR 14.7)), all had psychiatric co-morbidities and most had a poor socio-economic status. 91/145 (62.8%) reported ongoing intravenous drug use. So far, SVR has been achieved in 100% according to mITT analysis (n = 79/79) with n = 11/145 (7.6%) patients being lost to follow-up (FU) and n = 55/145 (37.9%) currently on treatment. 5 patients showed HCV reinfection after achieving SVR12.
SS-patients achieved SVR in 93.8% according to mITT analysis (n = 76/81) with n = 8/105 (7.6%) patients being lost to FU and n = 16/105 (15.2%) currently on treatment. 3 patients experienced HCV relapse after treatment with SOF/VEL and n = 2 died for reasons not related to therapy. No reinfections were recorded in the SS-group.
Conclusion: SOF/VEL given as DOT along with OST in PWIDs with a high risk of non-adherence to antiviral therapy resulted in excellent SVR rates (100% according to mITT) similar to patients with presumed "excellent compliance" under standard drug intake. Thus, HCV treatment with DAA using the concept of DOT seems to be an effective HCV-elimination strategy among the high-prevalence population of PWIDs on OST.

THU444

Externalized HCV linkage-to-care cascade in the biggest harm reduction center in Barcelona: approaching a high-risk PWID population

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Background and Aims: Significant scale-up of treatment among people who inject drugs (PWID) is necessary to achieve WHO hepatitis C virus (HCV) elimination targets. PWID with ongoing high risk practices are the most difficult-to-reach population. We tested whether active PWID could be recruited and treated successfully through a externalized hepatology outpatient clinic at the biggest harm reduction center (HRC) in Barcelona.
Method: On site HCV point-of-care screening for HCV-IgG antibody and HCV-RNA (GenXpert®), liver stiffness measurement (LSM), antiviral therapy delivery and sustained virological response (SVR12) assessment were performed at the HRC. Dried blood spot (DBS) was collected at baseline, SVR12 and every 6 months in order to differentiate relapse vs reinfection. Adherence was assessed by daily or weekly visits. The program included educative and harm-reduction interventions.
Results: So far 443 individuals have been prospectively enrolled. Of these, 265 (58%) accepted HCV screening, of whom 172 (65%) were HCV-RNA positive. Of the 112 (65%) individuals who have already started treatment, median (P_{25}-P_{75}) age was 42 years (35–47), 87% were male, 34% foreigners, 37% homeless, 73% unemployed and 62% had been imprisoned before. At enrolment, 67% injected daily (51% more than once a day) although 39% were also on opiate substitution therapy. In regard to high risk practices, 30% reported either needle or paraphernalia sharing and 44% unprotected sexual relationships. Concomitant alcohol consumption was reported in 37% [4(2–8) units/day]. Baseline LSM values were 6.3 (4.9–7.8) kPa with 14% patients having advanced fibrosis (>9.5 kPa). All patients received pan-genotypic antiviral therapy either 8 or 12 weeks. Preliminary results showed >80% treatment adherence in the majority of patients (71%) and SVR12 rate of 70% with no difference regarding type or duration of antiviral therapy. Preliminary reinfection rate was 12%. Active injecting persisted in 90% of treated individuals, but the injecting frequency decreased from a daily to a weekly basis (or less) in 40% of them. Interestingly, unemployment rate decreased significantly (>50%) in treated individuals.
Conclusion: This patient-centered circuit demonstrates that HCV treatment can be successfully delivered to active PWID with high-risk practices. Besides HCV elimination, therapy might have a benefit on drug consumption habits and social inclusion, supporting the role of educative interventions.

THU445

In-depth molecular characterization of inherently resistant African HCV genotype 1, subtype 1l, in patients failing DAA-based therapy

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Background and Aims: So-called "unusual" HCV genotype 1, subtype 1l (GT-1l) is common among HCV-infected patients of African origin. GT-1l has recently been suggested to be less responsive to NS5A inhibitor-containing regimens than GT-1a or GT-1b. Here, we used shotgun metagenomics based on deep sequencing to generate full-length HCV genome sequences and characterize amino acid substitutions present at baseline and selected by DAA therapy in

regions targeted and not targeted by DAAs in GT-1l infected patients who failed to achieve SVR.
Method: Shotgun metagenomics were used to generate full-length HCV GT-1l genome sequences. Briefly, library preparation was performed using Total RNA and Nextera XT kit (Illumina). Deep sequencing was performed by means of NextSeq500 (Illumina). Full-length HCV sequences were analyzed using our original in-house MetaMIC® software (1% cutoff).
Results: Among 771 patients with HCV infection, treated with DAAs who experienced a virological failure and were referred to our center between 2015 and 2019, 316 (41.0%) were infected with genotype 1, and 20 of them (6.3%) with GT-1l. All GT-1l-infected patients were of African origin. Deep sequencing of full-length HCV GT-1l genomes was performed in 10 patients who failed SOF/LDV±RBV (n = 8, 80%), SOF/VEL (n = 1, 10%) and SOF/SIM (n = 1, 10%).
At baseline, all of the 10 GT-1l patients had ≥ 3 dominant NS5A resistance-associated substitutions (RASs), including K24G/S (>99%), L31M (>99%) and H58P (>99%). Additionally, baseline NS5A-Q30R was present in 3 patients (>99% in 2 patients; 25% in 1 patient). Sequential analysis of full-length HCV genome sequences showed enrichment of NS5A-Q30R in one patient at failure (>99%) and the selection of NS5A RASs in other patients: baseline K24S (8% and 40%, respectively) replaced by K24G (>99%) in 2 patients; selection of Y93F and Y93H RASs at failure in 2 other patients (20% and 40% respectively).
No NS5B RASs were detected. NS3 R155K was selected in a patient failing SOF/SIM (30%). No particular amino acid changes were observed between baseline and failure in genome regions other than those targeted by the HCV DAAs administered.
Two patients were retreated with SOF/VEL/VOX and both achieved SVR.
Conclusion: We report the largest cohort of African GT-1l-infected patients failing DAAs thus far. The large number of NS5A RASs present at baseline explains lower SVR rates with NS5A inhibitor-based therapies in these patients. Our results emphasize the need for identification of this subtype and other "unusual" subtypes (e.g. GT-4r) in Africa where they are common, and the requirement for equity of access to last-generation DAA therapies in Africa.

THU446

Reasons for direct acting antiviral failure in patients referred for multi-disciplinary team discussion and virological outcomes of retreatment

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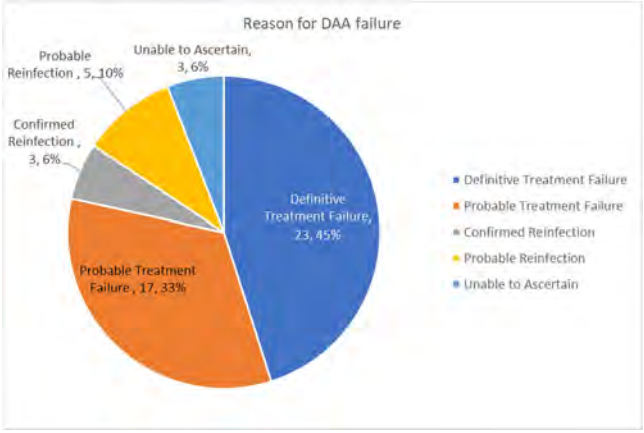
Background and Aims: NHS (National Health Service) Greater Glasgow and Clyde HCV (Hepatitis C virus) DAA (Direct Acting Antivirals) Treatment Failure MDT (Multi-Disciplinary Team meeting) provides regional advice service for retreatment of patients who previously failed DAA therapy and were not obviously re-infected. This is a service evaluation study to establish the reasons for DAA treatment failure, whether MDT advice was followed, and the virological outcome of retreatment.
Method: All referrals made to the HCV DAA Failure MDT service between April 2017 and March 2019 were retrospectively evaluated. Patients' pre- and post-treatment HCV Genotype, resistance-associated variants (RAVs) tested by population-based sequencing, risk of reinfection defined by documented history of intravenous drug abuse, and compliance with initial treatment regimen were all taken into account when deciding on the reason for DAA failure. Referred cases were categorized into 5 groups: Definitive Treatment Failure (DTF), Probable Treatment Failure (PTR), Confirmed Reinfection (CRI), Probable Reinfection (PRI), and Unable to Ascertain (UA).



Results: After excluding one case due to a pre-analytical diagnostic error, and seven cases due to a lack of documentation, a cohort of 51 eligible patients was identified. The majority of patients discussed had either DTF (45%) or PTF (33%) with relatively few cases of suspected reinfection (figure 1). New RAVs were identified in 22 (96%) of DTF cases. The MDT provided retreatment recommendations for 49 patients and advised against retreatment in 2 cases, both of whom subsequently died. Of the 49 patients, 42 (86%) received a second DAA course, 5 (10%) were lost to follow-up, 2 (4%) died prior to starting retreatment. MDT recommendations were followed in 37 (88%). At the time of writing, 23 (55%) patients had a test for sustained virological response (SVR) at week 12 or later and 21 (91%) of them remained negative for HCV. A further 14 (33%) had not yet been tested for SVR at week 12, and 4 (10%) were still undergoing retreatment.
Conclusion: Most cases referred to the HCV DAA Failure MDT service in NHS Greater Glasgow and Clyde are considered to have definitively or probably failed their treatment. The majority of patients received retreatment in line with the MDT advice. Successful retreatment can be achieved in a very high proportion of these patients.

THU447

Microelimination beyond prison walls: subjects sentenced to non-custodial sentences, screening and immediate assisted treatment with "navigator" figure and telemedicine

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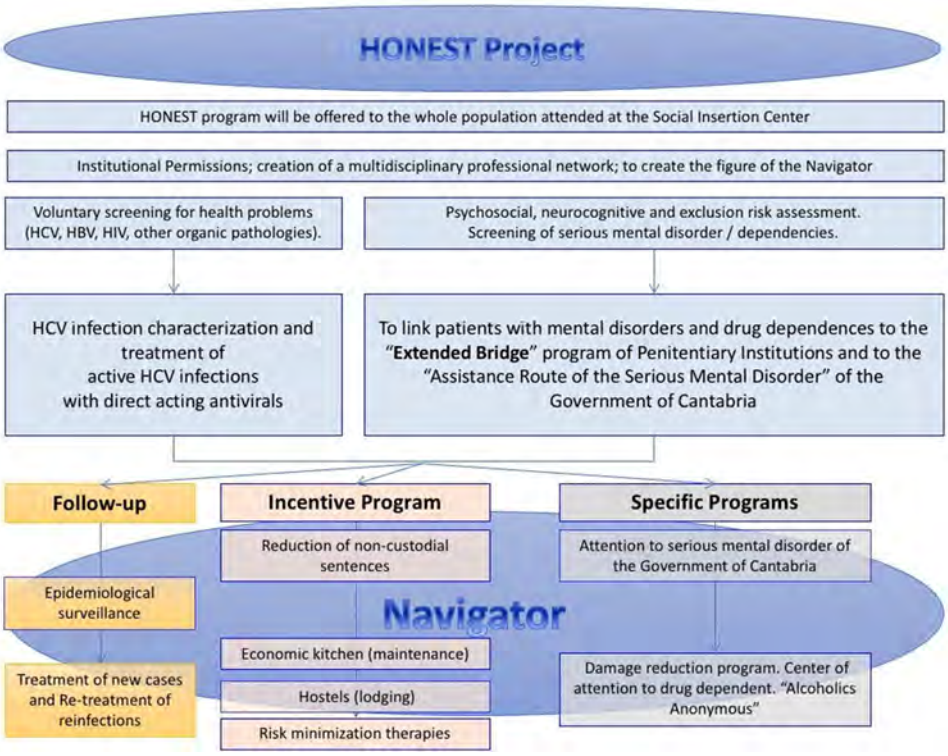
Background and Aims: The Spanish prison population includes two groups: inmates admitted in prison and those who are serving non-custodial sentences. The latter has not yet been studied. The aims of this study are: 1.- To describe this population at social, educational, medical levels and psychiatric comorbidities. 2.- To systematically screen and to treat HCV infection in this population. 3.- To engage this people with health care programs for the management of medical, psychiatric and social conditions.



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Method: Prospective observational study, including all subjects sentenced to non-custodial sentences attended at the Center for Social Insertion "José Hierro" (Santander) from June 2019 to June 2021, between 18 and 79 years and who gave signed informed consent. Assisted by the medical team and the center's "Navigator," systematic screening of HCV is performed by detection of antibodies by Oraquick®, those that are positive, viral load is determined by GeneXpert® in capillary blood. All cases with detectable viral load are evaluated by the hepatology staff by telemedicine and then antiviral treatment is prescribed. Thus, active HCV infection detection, disease evaluation and treatment are all done in the same day. The Navigator figure facilitates continuity for medical care and social assistance of these individuals (accompaniment to the hospital, adherence to treatment etc.)

Results: So far, 327 people have been invited to participate, 308 of them have been screened for HCV (94.2% acceptance). The prevalence of anti-HCV + has been 7.8% (24), which represents 5 times the general population. The prevalence of detectable viral load is 3.2% (10), above 10 times the prevalence of viremia in the community. All patients have initiated antiviral treatment either in the hepatology or infectious unit in case of HIV co-infected. Regarding comorbidities: problems related to substance abuse were detected in 148 (48%), suspected serious mental disorder in 25 (8.1%), previous stay in prison in 60 (19.5%). Currently, navigator is monitoring 54 (16.5%) patients regarding HCV treatment and their comorbidities.

Conclusion: The population serving non-custodial sentences is a challenging group, difficult to approach and with a high prevalence of HCV infection. Microelimination programs such as this, using rapid diagnostic tests, telemedicine and "the Navigator" figure are necessary in these vulnerable and hard to reach populations.

THU448

Efficacy of sofosbuvir/velpatasvir (s/v): impact of treatment adherence

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Background and Aims: Current all-oral regimens offer the promise of cure for nearly all Canadians living with chronic HCV infection. This is particularly true with the availability of simple pan-genotypic regimens such as sofosbuvir/velpatasvir (S/V), administered as one tablet once a day for 12 weeks for the treatment of all HCV genotypes and all levels of fibrosis. Clinical trial results suggest these regimens are associated with very high cure rates, even in the setting of sub-optimal adherence. There is limited real-world evidence to substantiate these findings.

Method: Accessing the national observational Canadian Network Undertaking Against Hepatitis C (CANUHC) database, we evaluated

all patients receiving S/V for the treatment of chronic HCV infection. The endpoint of this analysis was the achievement of a cure of HCV infection (undetectable HCV RNA levels 12 or more weeks after the end of therapy, SVR12) as a function of the reported level of adherence to therapy that was achieved.

Results: A total of 152 individuals were included in this analysis, with an overall SVR12 rate of 98.7% (150/152). Overall adherence >90% was reported in 142 (93.4%) participants, with 10 (6.6%) reporting adherence below 90%, 3 of which (2%) were below 75%. Of those with <90% adherence, all achieved SVR12. Subjects with sub-optimal adherence (n = 10) differed slightly from the entire cohort by mean age (46.5 vs 50.4 years), sex (30% vs. 41% female), HCV genotype (50% vs. 45% GT3) HIV co-infection status (20% vs. 14%), history of injection drug use (70% vs. 47%) and mean fibrosis score (10.9 vs. 9.3 kPa). Two individuals did not achieve SVR12 (both virologic relapses), both within the >90% adherence group. Non-SVR subjects were 69 and 44 years old, both were female, fibrosis scores were 4.5 kPa and 8.2 kPa, one each GT2 and GT3. One individual had a history of injection drug use and neither had any documentation of treatment interruption >7 days or premature treatment discontinuation.

Conclusion: Within the CANUHC cohort, self-reported adherence was generally high, as was the rate of achievement of SVR12 with the use of S/V. Suboptimal adherence was rare and not associated with treatment failure nor with any specific demographic profile. These data endorse the relative robustness of the S/V regimen in clinical practice and is reassuring as the use of S/V is expanded into populations facing multiple obstacles to treatment adherence.

THU449

Final challenges: real-world experience with sofosbuvir, velpatasvir and voxilaprevir in patients with advanced cirrhosis

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Background and Aims: In clinical trials, salvage therapy including Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX) achieved an SVR12 rate of 96% in NS5A-experienced participants. An extended access program (EAP) for SOF/VEL/VOX was sponsored by Gilead Pharmaceuticals for Australian patients with advanced liver disease or prior liver transplantation (LT), who had relapsed. We determined the real-world efficacy and safety of this regimen in this cohort with advanced liver disease.

Method: In this Australian multicentre EAP study, adult patients with chronic HCV infection genotype(GT)1–6 with prior failure on a DAA NS5A inhibitor containing regimen were eligible to access 12 weeks of SOF/VEL/VOX 400 mg/100 mg/100 mg. Other eligibility criteria included compensated liver disease with at least one of the following i) Child Pugh (CP)A cirrhosis with clinically significant portal hypertension or platelets $<100 \times 10^9$/L, ii) prior LT, or iii) severe extra hepatic manifestations. Hospitals with >1 EAP recipient were invited to participate. Clinical characteristics and treatment outcomes were recorded at baseline, end-of-treatment (EOT) and SVR12. HCV NS5A RAS testing was performed prior to retreatment, where serum was available. The primary outcomes was SVR12 rate.

Results: To date, baseline data is available for 89 patients from 24 participating hospitals. 85 have reached end-of-treatment (EOT), and 80 have SVR12 data available for analysis. Four patients have incomplete data due to early discontinuation of therapy (n = 2), loss to follow up (n = 1) and death (n = 1). 74 (83%) were male and the median age was 53. GT3 was the most common (n = 64), then GT1a (n = 18), GT1b (n = 4), GT6 (n = 2) and GT4 (n = 1). The median platelet count was 127. 68 (75%) had cirrhosis and of these, 35 (51%) had portal hypertension. 14 (16%) had prior hepatoma and 15 (17%) prior LT. All participants were NS5A-experienced and 8 (9%) had received >1 DAA course (1–4). Three participants were treated with a "lead-in" regimen of SOF + NS5A-inhibitor to optimise liver function before switching to SOF/VEL/VOX. SVR12 rates are shown in table 1. Treatment was generally well tolerated with mild AEs (n = 13/80, 16%), however two participants with CPA cirrhosis at baseline experienced hepatic decompensation. One *de novo* and two recurrent hepatomas were identified. Data collection is ongoing.

Table 1	Overall	GT3	GT1a	GT1b	GT6
Cirrhotic	89% (56/63)	89% (42/47)	100% (10/10)	50% (2/4)	100% (2/2)
LT/non cirrhotic	94% (16/17)	92% (11/12)	100% (5/5)		

Conclusion: This is the first Australian study to assess the real-world efficacy and safety of SOF/VEL/VOX amongst patients with advanced liver disease. SVR12 rates were good, but data suggests there remain a small number of very hard to cure patients, particularly those with GT3 and advanced disease, suggesting a need to explore strategies to optimise SVR in these groups.

THU450

Management of hepatitis C in primary healthcare in the country of Georgia

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Background and Aims: In April 2015, with a partnership with Gilead Sciences and technical assistance from U.S. CDC, Georgia launched the world's first hepatitis C elimination program. By August 30, 2019, more than 60 thousand persons initiated treatment, achieving >98% cure rates. Broad access to direct acting antivirals (DAAs) resulted in rapid increase in treatment uptake in 2016, which has since declined due to barriers in diagnosis and linkage to care. To address this issue Georgia initiated service decentralization in 2018 by integrating hepatitis C virus (HCV) screening and treatment in primary healthcare centers (PHCs). We report preliminary results of an integrated model of HCV care in PHCs from August 2018 through August 2019.
Method: By August 31 2019, a total of 10 PHCs provided HCV care services throughout the country. The integrated model was based on a "one stop shop" approach, by which patients received all HCV screening, treatment and care services at the PHCs. PHCs provided care to HCV treatment-naïve patients with no or mild fibrosis (FIB-4 score<1.45) using simplified diagnostics and a treatment monitoring approach, while persons with advanced liver fibrosis/cirrhosis were referred to specialized clinics. Patients received Sofosbuvir/Ledipasvir and/or Sofosbuvir/Velpatasvir for 12 weeks. Sustained virological response (SVR) was defined as undetectable HCV RNA 12–24 weeks after end of therapy. The Extension for Community Healthcare Outcomes (ECHO) telemedicine model was utilized to train and support primary healthcare providers. Regular teleECHO videoconferencing was conducted to provide primary care providers with advice and clinical mentoring.
Results: Among persons diagnosed with active HCV infection, 639 were evaluated for FIB-4 score. Of these, 436 (68.2%) had FIB4 score<1.45; of them 355 (81.4%) initiated treatment. A total of 241 patients completed treatment. Of 146 patients within the 12–24 week window of SVR eligibility, 108 had been tested at the time of analysis, and 107 achieved SVR (99.1% cure rate).
Conclusion: Our study reported the feasibility and effectiveness of integrating a simplified HCV diagnostic and treatment model in PHCs. Countrywide expansion of this model is warranted to bridge the gaps in the HCV care continuum and ensure high rates of treatment uptake towards achieving elimination targets.

THU451

HCV DAA treatment failure is associated to hepatocellular carcinioma presence

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Background and Aims: Sustained Virological Responses (SVR) are nowaday obtained in real life settings, in almost 98–99% of HCV-infected patients using 8 or 12W schedules and 2nd generation DAAs (glecaprevir/pibrentasvir, sofosbuvir/velpatasvir and elbasvir/gazoprevir). Clinical or virological predictors of viral failures with both 1st and 2nd generation DAAs are poorly understood.
Method: Between April 2015 and April 2019, 2508 patient received DAAs for HCV at our Institution. A retrospective analysis of the Virology Laboratory Database was performed to identify all the patients who completed the DAA treatment schedule, having HCV-RNA detectable 24 weeks or later after end-of treatment (EOT). Such cases were considered as viral failures (VF). Clinical features of the subjects with VF were recorded in a dataset: demographic, BMI, HCV genotype, basal Viral load, HIV status, Metavir stage, previous HCV treatment experience, type of DAA and presence of HCC (Li-RADS 4 or 5, identified before DAA, or during the 18 months following EOT). Several parameters were compared between 1st and 2nd generation DAA VF, and between subjects with VF or SVR. This latter group included 519 consecutive subjects with SVR, treated at our Unit during the same interval of time.
Results: The global SVR24 rate at our Institution was 97.1% (73/2508). Fifty-nine patients experienced failure with first generation DAA, and 14 with 2nd generation DAAs (Table 1). Viral relapses occurred in 49.4% of the cases already at post treatment (PT)W4 (n.36), 37.0% between PTW4 and PTW12 (n.27), 6.8% between PTW12 and PTW24 (n.5) and 6.8% (n.5) after PTW24.
Sixty out of the 73 subjects with viral relapse where submitted to a second DAA course with 100% of SVR12. Patients with VF showed high association (35.6%) to a concomitant HCC, reaching high statistical significance when compared to patient with SVR observed during the same time period at our Unit (Table 2). Significance persisted even when VFs were compared with only cirrhotic patients with SVR (n 175, p = 0.04).

	Pts with Virological Failure n. 73		Pts with Sustained Virological Response n. 519		p
Age (mean, SD)	56.8 yrs	8.9	59.4 yrs	10.4	0.524
Male Gender (n, %)	65	89.0%	319	61.4%	**0.0001**
HCV Genotype 1a or 3 (n, %)	46	63.0%	281	54.1%	0.168
HCC diagnosis (n, %)	26	35.6%	39	7.5%	**0.0001**
Liver Cirrhosis (F4)	49	67.1%	230	44.3%	**0.0003**

Conclusion: The presence of HCC and cirrhosis independently increase the risk of HCV treatment failure with DAAs.

THU452

Challenges in hepatitis C elimination despite highly effective antiviral agents - experience of a tertiary hepatology centre

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Table 1: (abstract: THU451)

Pts with Virological Failure	Total		1st generation DAAs		2nd generation DAA		P
	n. 73		n. 59		n. 14		
Age (mean, SD)	56.8 yrs	8.9	55.5 yrs	7.1	62.8 yrs	11.0	**0.003**
Male Gender (n, %)	65	89.0%	53	89.8%	12	85,7	0.645
HCV Genotype 1a or 3 (n, %)	46	63.0%	38	64.4%	8	66.7%	0.759
Basal HCV-RNA log (mean, SD)	6.23	6.45	6.12	6.38	6.44	6.60	0.867
HIV-Ab+ status (n, %)	26	35.6%	22	37.3%	4	28.6%	0.758
Liver Cirrhosis (n, %)	49	67.1%	43	72.9%	6	42.9%	0.055
HCC diagnosis (n, %)	26	35.6%	23	39.0%	3	21.4%	0.352

	PWIDs (n=234)	Non-PWIDs (n=197)
Positive viral load	n=206 (88%)	n=192 (97.4%)
HCV genotype	3: n=97 (48.1%) 1a: n=67 (33.1%) 1b: n=18 (8.9%)	1b: n=85 (44.5%) 1a: n=52 (27.2%) 3: n=24 (12.5%)
First therapy regime: -PegInterferon (PegIFN)+Ribavirin -DAA+PegIFN+Ribavirin -DAA+Ribavirin -DAA	 n=12 (7.2%) n=5 (3%) n=23 (13.9%) n=126 (75.9%)	 n=1 (0.6%) n=5 (2.8%) n=49 (28%) n=120 (68.6%)
Reinfection	n=9 (4.3%)	n=0 (0%)
Currently therapy status -SVR - Viral load negative by end of (EOT), but patients did not show up to SVR12 visit - Viral load negative at EOT and SVR12 visit will follow - Therapy discontinued -Relapse (without further therapy) -Under therapy -without therapy	 n=97 (47.2%) n=47 (22.8%) n=11 (5.3%) n=2 (0.9%) n=0 (0%) n=9 (4.4%) n=40 (19.4%)	 n=151 (78.7%) n=10 (5.3%) n=7 (3.6%) n=1 (0.5%) n=2 (1%) n=4 (2%) n=17 (8.9%)

Figure: (abstract: THU452)

Background and Aims: Hepatitis C therapy with directly-acting antiviral agents (DAA) (especially pangenotypic regimens) in a real-world setting is associated with sustained virological response (SVR) >95% with almost no adverse events. The World Health Association published a strategy to eliminate hepatitis C by 2030, but in daily practice this can be difficult to achieve in some patients, especially in people who inject drugs (PWIDs). The **aim** of this study was to investigate the adherence to treatment, SVR rate, and reinfection rate in hepatitis C patients with and without intravenous drug use.
Method: Our retrospective study included patients with hepatitis C, which were evaluated in our Hepatology outpatient's clinic between 01/2014–08/2019.
The following information were extracted from patients file: presence of positive viral load, active and recent (in the last six months) use of i. v. drugs, HCV genotype, treatment regimen, SVR, reinfection with hepatitis C virus, HIV coinfection, ongoing opioid substitution therapy (OST).
Results: We included 431 hepatitis C patients (234 PWIDs and 197 non-PWIDs).
PWIDs were younger as compared with non-PWIDs: 31 ± 9.6 vs 58.8 ± 13.8 years, p < 0.0001. The percentage of men was higher in the PWIDs as compared with non-PWIDs group: 71.8% vs. 55.4%, p = 0.0006.
HIV coinfection rate was similar between the two cohorts: 0.8% vs. 1%, p = 0.76.
Positive viral load rate was lower in the PWIDs group. Genotype 1b was predominant in patients without iv drug use, while genotype 3 was more common in the PWIDs group. Most of the patients were treated with DAAs only (Figure).
The proportion of patients not starting therapy was significantly higher in the PWIDs cohort: 19.4% vs. 8.9%, p = 0.003. Non-compliance (did not show up to start therapy) rate or refusal of therapy was also significantly higher in the PWIDs cohort: 15% vs. 6.7%, p = 0.01.
In the PWIDs cohort, younger age and recent (in the last 6 months) or ongoing i.v. drug use was associated with non-compliance: 31.1 ± 8.4 vs. 35.8 ± 10.6 years, p = 0.02 and 33.3% vs. 12.8% respectively, p = 0.0008.
Ongoing OST was associated with better compliance: 61.1% vs. 46.1%, p = 0.04.
Conclusion: To achieve hepatitis C elimination, better strategies especially regarding PWIDs are needed. In our cohort, around 14% of all the patients with positive viral load (and around 20% of PWIDs) were not able to be treated and still pose an ongoing risk for infection to the community.

THU453

Reasons for hepatitis C direct acting antiviral failure: experience from the field

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Background and Aims: Since HCV direct acting antiviral (DAA) disposal, successive national recommendations have been regularly published to optimise treatment efficacy and to homogenise practices. Adhesion to these guidelines led to an overall success of 97.4% in our university hospital setting, in line with other recently reported cure rates elsewhere. The aim of this study was to analyse the reasons for the rare observed treatment failures.
Method: A retrospective study based on data mining of 962 treatment lines started between January 2014 and April 2019 and leading to 937 (97.4%) sustained viral responses was conducted. Demographic and clinical characteristics of 23 (2.4%) patients who relapsed (RR) and 2 (0.2%) who presented a viral breakthrough were analyzed and compared to cured patients (SVR). HCV population sequencing was used to document genotype and resistance associated substitutions (RAS).
Results: Relapses were statistically more frequent before 2017 (3.4%) than after (1.2%; p = 0.033), and the unique failure observed in 2019 was attributed to a genotyping error leading to an inadequate treatment choice. Severe fibrosis was more frequent (56.5%) in RR than in SVR (27.7%; p = 0.004), however, cirrhotic patients were more frequently treated before 2017. Hepatocellular carcinoma was also linked to relapse (p = 0.03). Previous treatments with IFN +/– RBV did not influence treatment response, neither gender, age nor baseline viral load. Genotype 3 was not associated with relapse. By contrast, non-a/non-d genotype 4 subtypes (n = 29, 4r, p and k) were more

often found in relapsers (4/23; 17.3%) than in SVR (25/937; 2.7%; p = 0.015). In relation with these findings, to be of African ancestry was also associated with a 4 fold reduced rate of SVR (p = 0.0083). While poor compliance or reinfection could not be formally excluded, sequencing data performed on available viral strains (19/23) identified solely NS5A RAS but unremarkable NS3 and NS5B sequences. Noteworthy, only one patient (1/274; 0.36%) has relapsed since pangenotypic regimens have become available.
Conclusion: Despite an impressive overall efficacy in real-life setting, DAA treatments may present suboptimal response in rare situations that need to be finely characterized. As suggested in recent publications, infrequent HCV subtypes should be particularly scrutinized and could benefit from closer monitoring. Pangenotypic combinations are certainly the only choice to be recommended in these cases.

THU454

Effectiveness of new generation DAAs for HCV infection in a large cohort of Italian people who use drugs (PWID): the cleo-grecas real-world experience

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Background and Aims: HCV-infected people who use drugs (PWUD) is characterized by a low therapy adherence and often lost to follow-up when treated with directly acting antivirals (DAAs). Aim of our study was to evaluate the effectiveness of DAAs therapy in term of adherence and sustained virological response in a real-world setting as Italian PWUD, most of them strictly followed within a continuous interdisciplinary program with hepatologists included inside the Italian Centres for Drug Addicts (SerDs) widely distributed throughout the whole Italian territory.
Method: From July 2015 to April 2019, all consecutive HCV infected PWID were enrolled in a prospective observational real practice study (CLEO platform and RESIST Network); substances used were heroin 35.2%, cocaine 10.3%, opiates 8.6%; 44.8% were contemporary cocaine and heroin users. The majority of PWUD (80.9%) were routinely followed inside the Italian SerDs and on opiate substitution therapy (OST) with methadone 59.6%, buprenorphine 8.8%, naloxone plus buprenorphine 6.5%, naltrexone 20%. Treatments were often beginning inside the SerD Centres under strict prescription by the hepatologists, according the Italian national guidelines.
Results: One thousand three hundred eighty five patients, male 87.8%, mean age 49 (+/–9.47), 31% with liver cirrhosis, median basal HCV-RNA 122000 IU/ml completed treatment and were evaluated for the Sustained Virological Response at week 12 post-treatment (SVR-12); HCV genotypes: 1a = 34%, 1b = 11.28%, 2 = 2.88%, 3 = 42.3%, 4 = 9.3%, 7 = 0,17%. DAAs regimens: SOF/VEL 37.4%, GPR/PBR 36%, SOF/DCV14.4%, SOF/LDV 7,1%, EBR/GZR 5.1%. The overall SVR-12 rate was 95.51%; 2.63% relapsed; 0.77% were non responders; 0.70% dropped out, 0.39% stopped because of side effects. Patients undergoing treatment with 3rd generation DAAs (SOF/VEL, GPR/PBR,EBR/GZR) showed a SVR-12 rate higher than 2nd wave DAAs (97,5% vs 92,1%, p = 0.0002). HIV co-infected patients were 10% of total with a similar SVR-12 rate to that of HCV mono infected.
Conclusion: In this real-world setting of Italian HCV infected PWUD, a very high SVR-12 rate was observed, mostly due to the close cooperation between the healthcare workers in Italian SerDs and the hepatologists in the context of the interdisciplinary team. Low rate of drop-out was mainly due to the continuum of care programme inside SerDs. Our results launch this model as best practice to manage this kind of patients worldwide.

THU455

Hepatitis C positive organ transplantation to negative recipients at a multi-organ Canadian transplant centre: ready for prime time

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Background and Aims: Organ transplantation offers better survival for patients with end stage organ disease compared to no transplant. Hepatitis C virus (HCV) positive donor organ transplantation to negative recipients is a novel adopted strategy that may potentially increase the donor pool. The aim of this study is to evaluate our multiorgan transplant centre experience with transplanting HCV positive organs.
Method: This study was conducted at London Health Sciences Centre in London, Ontario, Canada. All transplants with HCV nucleic acid testing (NAT) positive and negative organs were included from 2018 to present. Our primary outcome was the rate of sustained virologic response at 12 weeks after the end of treatment (SVR12) in patients that developed viremia. Secondary outcomes were the rate of transmission of HCV in both NAT positive and negative recipients, treatment adverse events, and graft failure rate.
Results: A total of 27 organ transplantations with hepatitis C positive organs were performed including 19 kidneys (70.4%), 4 livers (14.8%), 2 kidney-pancreas (7.4%),1 liver-kidney (3.7%), and 1 heart (3.7%). The mean age of recipients was 48 ± 12 years. 54% of them were male. NAT positive HCV organs were 20 (74%) of the organs used and viremia was transmitted in 90% of these patients while no transmission occurred in NAT negative HCV organs. HCV genotype was 1a in 76%, 1b in 6%, 2 in 6%, and 3 in 12%. The most common direct acting antiviral (DAA) used for treatment was Ledipasvir/Sofosbuvir in 13%, Velpatasvir/Sofosbuvir in 62%, and Glecaprevir/Pibrentasvir in 25%. SVR12 was 100% in all patients that completed HCV therapy. Treatment was tolerated by all patients, there were no significant treatment adverse events, and there were no graft failures.

Conclusion: Using HCV positive organs is safe and may further expand the donor pool. In patients that have HCV transmission post-transplant DAAs are efficacious with no significant adverse events, intolerance, or graft failure.

Liver tumours: Clinical aspects except therapy

THU458

Neutrophil-lymphocyte ratio predicts the risk of developing hepatocellular carcinoma in cirrhotic patients with chronic hepatitis B under antiviral therapy

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Background and Aims: The relationship between neutrophil-lymphocyte ratio (NLR) and hepatocellular carcinoma (HCC) development in cirrhotic patients with chronic hepatitis B is inadequately clarified. The objective of this study was to validate the predictive value of baseline NLR for HCC development in cirrhotic patients with chronic hepatitis B within three-year under antiviral therapy.

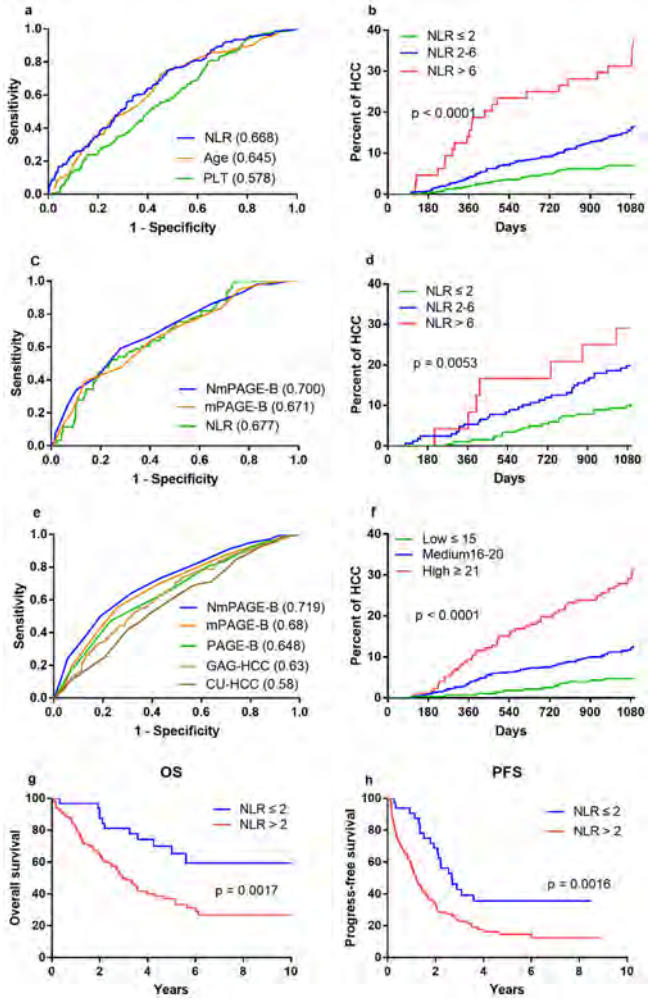

Figure: (a) AUROCs of the predictive value of the variables on HCC development during the 3-year follow-up in the derivation cohort. (b) Risk stratification of HCC development according to NLR with different cut-off (≤2, 2–6 and >6) in the derivation cohort ($p < 0.0001$). (c) AUROCs of NLR and risk models for the prediction of HCC development within 3 years in the validation cohort. (d) Risk stratification of HCC development according to NLR scores ($p = 0.0053$) in the validation cohort. (e) AUROCs of new model and other models for prediction of HCC in the derivation cohort ($p < 0.05$ for all, by log-rank test). (f) Cumulative incidence rates of HCC in the derivation cohort according to new model ($p < 0.0001$). (g) Kaplan-Meier curve analysis showing OS in HCC patients. (h) Kaplan-Meier curve analysis showing PFS in HCC patients. AUROC, time-dependent area under receiver operating characteristic; HCC, hepatocellular carcinoma; NLR, neutrophil-lymphocyte ratio; OS, overall survival; PFS, progress-free survival.

Method: In the retrospective analysis, a total of 1049 patients in the derivation group and 396 patients in the verification group were recruited. The independent factors of HCC development were determined using univariate and multivariate analyses. Optimal cut-offs were identified by calculating the Youden Index. Time-dependent area under receiver operating characteristic (AUROC) curve analysis was performed. The predictive value of NLR was assessed by Kaplan–Meier curves.
Results: The three-year cumulative HCC incidence rates were 13.5% and 15.4% in the derivation and validation group, respectively. Multivariate analyses showed that age, NLR and platelets were associated with HCC development. The AUROC for NLR was 0.668 (95% CI 0.622–0.713). Baseline NLR ≤ 2 predicted lower HCC development and NLR >6 is higher incidence of HCC ($p < 0.0001$). Moreover, NLR >2 was related to worse overall survival (OS) ($p = 0.0017$) and progress-free survival (PFS) ($p = 0.0016$) compared to those with NLR ≤ 2 in HCC group. Incorporation of NLR into a modified PAGE-B (mPAGE-B) model improved the predictive value for HCC development within three years (AUROC = 0.719).
Conclusion: Baseline NLR, an inexpensive blood count and routinely accessible inflammatory biomarker, may be a novel predictive marker of the three-year HCC risk in cirrhotic patients with chronic hepatitis B under antiviral therapy.

THU459

Differentiation and management of hepatobiliary mucinous cystic neoplasms: a single-center experience for 10 years

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Background and Aims: Hepatobiliary mucinous cystic neoplasms (H-MCNs) are quite rare cystic neoplasms of the liver. The management and outcome of the hepatic simple cyst (HSC) and H-MCNs are really different. However, the differential diagnosis of H-MCNs remains big challenging. Our aim is to present our experience and provide a preoperative H-MCNs risk prediction nomogram for differentiating H-MCNs from HSC.
Method: A retrospective study included 29 patients diagnosed with H-MCNs in pathology and 75 patients with HSC from June 2011 to June 2019 in Zhejiang University, School of medicine affiliated Sir Run-Run Shaw Hospital. Preoperative clinical data and outcome of surgery in H-MCN and HSC patients were analyzed.
Results: US, CT and MRI could accurately diagnose only 3.4%, 46.1% and 57.1% of H-MCNs, respectively. After univariate analysis and multivariate logistic regression analysis, the preoperative variables associated with H-MCNs were "enhancement after contrast" ($p = 0.009$), "located in the left lobe" ($p = 0.02$) and "biliary ductal dilation" ($p = 0.027$). A H-MCN risk predictive nomogram constructed by those factors and serum CA199 level showed an excellent discrimination (areas under the receiver operating characteristic curve were 0.940) and agreement calibration between predicted and actual probability.
Conclusion: Among patients with the H-MCNs, location of the tumor, enhancement in CT scan and biliary ductal dilation are significantly

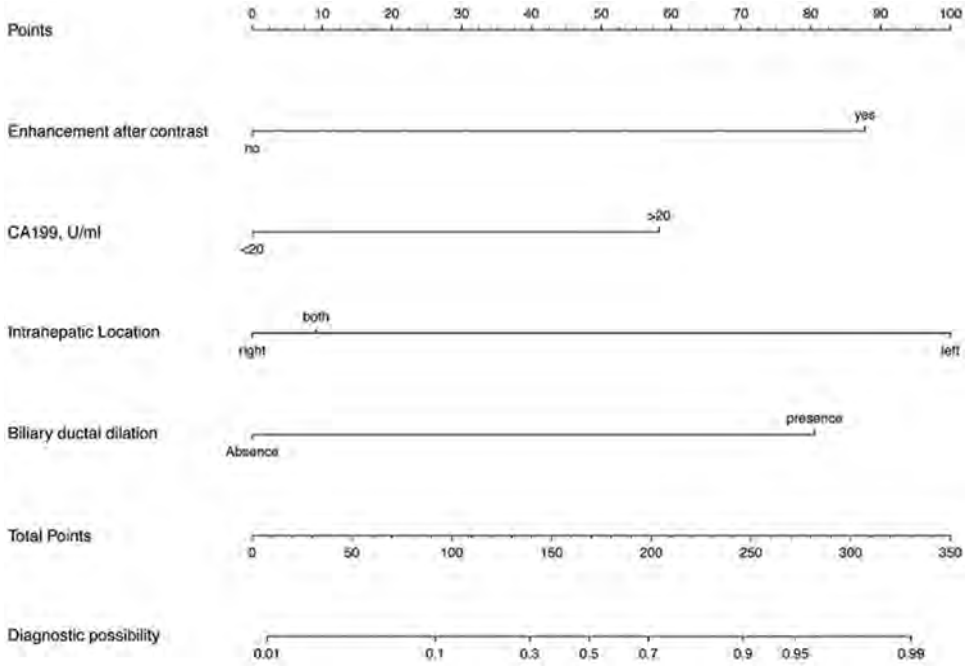

Figure 1. **A nomogram to estimate the possibility of H-MCN in liver cystic lesion.** To use this nomogram, find the position of the variables on the corresponding axis, draw a vertical line to the points axis to get the points of the variable. Calculate the total points of all variables and draw a line from corresponding total points axis to the possibility axis to get the probability of the H-MCNs.

independent risk factors. The reasonable treatment of H-MCNs are radical resection. Using of our nomogram could facilitate screening and identification of patients with liver cystic lesions.

THU460

Prognostic significance of systemic immune-inflammation index in patients with intrahepatic cholangiocarcinoma undergoing hepatic resection

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Background and Aims: The systemic immune-inflammation index (SII) is an index which incorporates platelets, neutrophils and lymphocytes, calculating by multiplying platelet counts by NLR. No data exists until now, evaluating the prognostic value of SII for ICC. This study aimed to investigate the prognostic effect of SII to predict long-term outcomes in patients with intrahepatic cholangiocarcinoma (ICC) undergoing hepatic resection.
Method: Consecutive ICC patients who underwent initial hepatectomy with curative intent from January 2009 to September 2017 were retrospectively reviewed. Receiver-operating characteristic (ROC) curves were used to determine the optimal cut-off values of SII. Kaplan-Meier curves and Cox proportional hazards regression were performed to evaluate the discriminative ability of preoperative SII in predicting overall survival (OS) and recurrence-free survival (RFS).
Results: A total of 530 patients were included and randomly divided into derivation (n = 265) and validation cohort (n = 265). The optimal cut-off value for SII was 450. At a median follow-up of 18 months (range, 1–115.4 months), 317 (59.8%) patients died and 381 (71.9%) patients experienced tumor relapse. Low SII level was associated with better OS and RFS (both $p < 0.05$). Multivariate analyses identified multiple tumors, node invasion and high SII level as independent risk factors for OS, while multiple tumors, node invasion and high SII level were identified as independent risk factors for RFS. Validation cohort confirmed the findings of derivation cohort.
Conclusion: The present study demonstrated the feasibility of preoperative SII as a prognostic indicator for ICC. Patients with increased SII level were associated with worse OS and earlier tumor recurrence. The SII level was an independent risk factor for OS and RFS in patients with ICC after hepatectomy. In the future, the SII could help stratifying patients with ICC, thus guiding therapeutic choices, especially in immunotherapy.

THU461

Serum and urine extracellular vesicles contain specific RNAs with diagnostic capacity for cholangiocarcinoma, being possibly involved in disease pathogenesis

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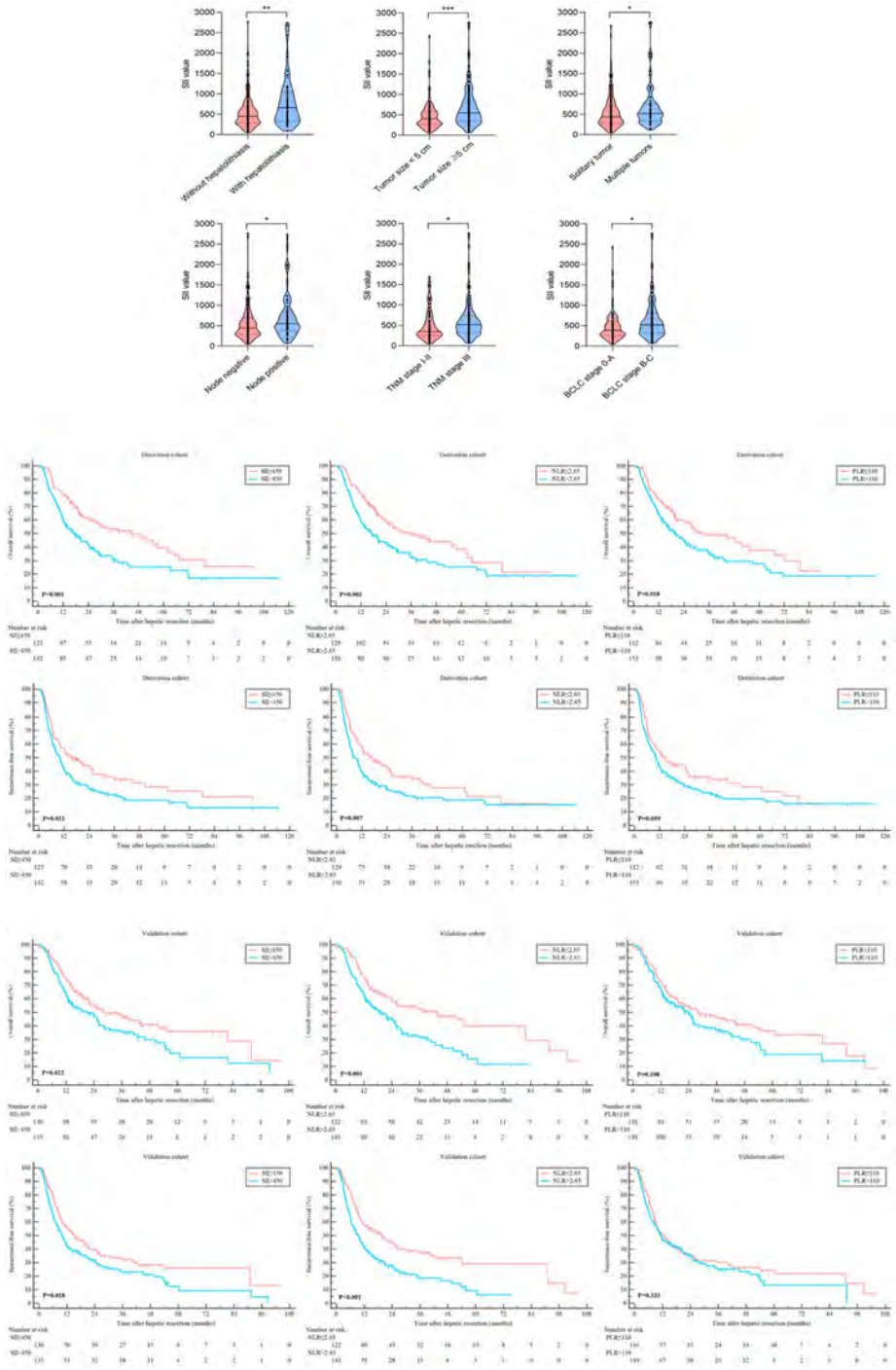

Figure: (abstract: THU460)

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Background and Aims: Cholangiocarcinoma (CCA) represents a heterogeneous group of biliary cancers with poor prognosis. The etiology of the majority of CCAs is unknown, but there are some risk factors that predispose to its development, such as the presence of primary sclerosing cholangitis (PSC). Simultaneously, around 80% of patients with PSC have concomitant inflammatory bowel disease, mainly ulcerative colitis (UC). Up to now, there are no specific and sensitive biomarkers for the non-invasive diagnosis of CCA. In this sense, extracellular vesicles (EVs) have been postulated as a source of biomarkers and possible pathogenic mediators of various diseases. Therefore, we propose to determine the potential value of serum and urine EVs as carriers of RNA biomarkers for the diagnosis of CCA and their possible involvement in CCA pathogenesis.

Method: Serum and urine EVs were isolated by differential ultracentrifugation from patients with UC (n = 8 and 12), PSC (n = 4 and 4) and CCA (n = 10 and 17) and from healthy individuals (n = 9 and 5). EV characterization was carried out through transmission electron microscopy (TEM), nanoparticle tracking analysis (NTA) and

immnunoblot. The content of EVs was determined by mRNA microarray-based transcriptomics (Illumina). The diagnostic value of identified transcripts [AUC, sensitivity, specificity, etc.] was calculated using IBM SPSS statistics. Finally, the expression of the selected candidates was evaluated in human CCA tumor and surrounding healthy tissue from two independent cohorts (TCGA and Copenhagen), as well as in cell cultures of normal human (NHC) and tumor cholangiocytes (EGI-1 and TFK-1) and in EVs released from those cell lines.

Results: Both isolated serum and urine EVs showed a rounded morphology (TEM), similar size (~180 nm in diameter, NTA) and typical EV markers (CD9, CD63 and CD81) by immunoblot. The transcriptomic analysis of these EVs showed a differential profile of RNAs in patients with CCA compared to healthy individuals or patients with other diseases (PSC and UC), with some of them presenting a high diagnostic value (AUC = 1). In patients with CCA, a total of 268 transcripts in serum and 50 in urine presented a differential abundance, and particularly 179 and 28 were found differentially expressed in CCA tumors (TCGA and Copenhagen), respectively. In addition, the expression of those transcripts also had altered RNA expression in CCA cells (49 mRNA) and in CCA cell-derived EVs (27 mRNA), presenting high diagnostic capacity (AUC = 0.92 CCA vs Ctrl) and possible being involved in the pathogenesis of the disease (e.g. cell growth, cell cycle, DNA repair, protein metabolism).

Conclusion: Serum and urine EVs of patients with CCA contain specific transcriptomic signatures with high diagnostic capacity, reflecting their potential use as non-invasive accurate biomarkers.

THU462

Novel protein biomarkers in serum extracellular vesicles for the diagnosis of cholangiocarcinoma (CCA) in patients with primary sclerosing cholangitis (PSC)

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Background and Aims: Cholangiocarcinoma (CCA) includes a heterogeneous group of biliary malignancies with very poor prognosis. Its etiology is generally unknown, although primary sclerosing cholangitis (PSC) constitutes a well-known risk factor. Currently, there are no non-invasive, early and accurate diagnostic methods for the diagnosis of CCA. In this sense, extracellular vesicles (EVs), biomolecule holders which are found in biological fluids, have recently emerged as a potential source of biomarkers for several diseases. Therefore, we aimed to characterize the protein content of serum EVs and determine the diagnostic value of EV-proteins as non-invasive biomarkers for CCA of unknown etiology and for patients who developed CCA on a PSC background.

Method: Serum EVs were isolated from patients with PSC (n = 39), CCA (n = 30; unknown etiology), PSC-CCA (n = 25) as well as from healthy individuals (n = 41) by differential ultracentrifugation. The characterization of the EV fraction was performed by transmission electron microscopy (TEM), nanoparticle tracking analysis (NTA, Nanosight) and immnunoblot. The protein content of these vesicles was determined by mass spectrometry-based proteomics. The diagnostic efficacy of the identified proteins was evaluated in two patient cohorts (analysis of ROC curves with IBM SPSS statistics). In addition, the expression (mRNA) of candidate biomarkers was evaluated in two independent cohorts of CCA tumor tissue and surrounding liver (TCGA and Copenhagen), as well as in CCA cell lines and normal cholangiocytes.

Results: Isolated EVs presented a round morphology (TEM), a similar diameter (180 nm; NTA) and typical markers of EVs such as CD9, CD63 and CD81 (immunoblot). By mass spectrometry, a total of 635 proteins were identified and proteomic analysis revealed a differential protein profile in patients with PSC, PSC-CCA, CCA, and healthy individuals. Certain identified proteins showed a high diagnostic value for CCA (increased PIGR: AUC 0.96, decreased HEP2: AUC 0.865), and for the diagnosis of CCA in patients with PSC (increased FIBG: AUC 0.859 and decreased HEMO AUC 0.859). Some of these proteins showed similar changes in CCA tumor tissue compared to surrounding liver, as well as in CCA cells compared to normal cholangiocytes.

Conclusion: Serum EVs contain accurate protein biomarkers for the diagnosis of CCA; with some of them being common for general CCAs and others specific for those with PSC etiology. The differential abundance of certain proteins in serum EVs constitute a promising non-invasive diagnostic tool and correlates with gene expression in tumor tissue and CCA cells, potentially playing a role in the pathogenesis of the disease.

THU463

Investigating the impact of extrahepatic metastasis in patients with HCC: does location matter?

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Background and Aims: Extrahepatic metastatic disease (EMD) in patients with hepatocellular carcinoma (HCC) leads to classification into advanced stage in which systemic therapy is recommended. However, data on the prognostic impact of EMD on overall survival (OS) in these patients is rare, especially when taking into account the exact location of extrahepatic metastases. Therefore, aim of this study was to determine the prognostic impact of EMD in general and with a focus on different EMD sites using a longitudinal approach.

Method: As the work-up of patients is still ongoing, so far 642 patients with HCC treated between 01/2005–01/2019 were extracted from the clinical registry of our tertiary referral center in order to reevaluate the impact of EMD. All cross sectional imaging studies were re-reviewed by a board certified radiologist specialized in HCC-imaging in order to determine date and location of EMD-development. Locations were classified into six categories: lymph nodes, peritoneum, lung, bone, adrenal gland, and others. Furthermore, the status of macrovascular invasion was determined.

Results: Of the 642 patients, 35 patients could not be evaluated due to concurrent malignant disease. Overall 124/607 patients developed EMD: 58 (47%) patients presented with EMD synchronous to initial HCC diagnosis, 66 (53%) patients had metachronous EMD. Median OS after initial diagnosis was 20.5 months for patients without and 11.7 months for patients with EMD ($p < 0.001$). The most common metastatic sites were: lymph node (n = 65), lung (n = 67), bone (n = 31), peritoneum (n = 26), adrenal gland (n = 18), and others (n = 12). Residual median OS after detection of lymph node, lung, bone, peritoneal, adrenal, brain, and other metastases was 6.2, 5.6, 4.8, 4.3, 4.7, and 5.6 months respectively. None of the sites were significantly

different. The incidence of macrovascular invasion in patients with EMD was significantly higher compared to the subgroup of patients without EMD (p < 0.001).

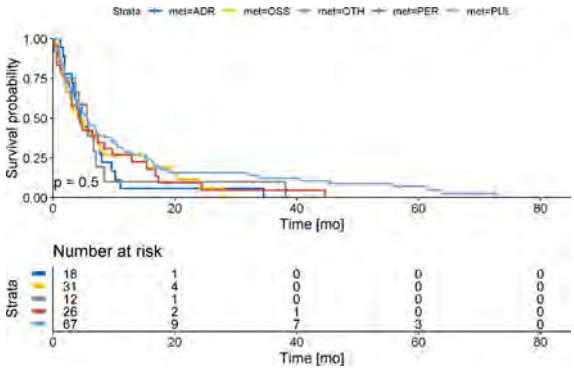

Figure: Overall survival of the different metastatic sites. ADR = adrenal; OSS = osseous; OTH = others; PER = peritoneal; PUL = pulmonary.

Conclusion: EMD had a significant impact on OS. However, there was no discernible difference in OS between metastatic sites. Therefore, under systemic treatment, the exact site is rather of secondary importance regarding OS. As EMD showed very strong correlation with macrovascular invasion, diagnosis of macrovascular invasion should prompt additional imaging in such patients.

THU464

Combination of AFP, AFP-l3 and PIVKA-II levels improves diagnostic accuracy of hepatocellular carcinoma (ALPS score)

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Background/Aims: We investigated the diagnostic performances of serum AFP, AFP-L3, PIVKA-II level, and the combination of these tumor markers for diagnosis of hepatocellular carcinoma (HCC).
Methods: Total 526 patients who underwent AFP and AFP-L3 tests were enrolled. We calculated the serum AFP-L3 level using the formula as follows: serum AFP-L3 level = serum AFP level (ng/mL) × serum AFP-L3 fraction (%) × 0.01. New diagnostic model, ALPs (**A**FP, AFP-**L**3 fraction, and **P**IVKA-II) score was developed as follows: ALP-II level = 1.7 × [serum AFP level (ng/mL) × AFP-L3 fraction (%) × 0.01] + 0.2 × PIVKA-II level (mAU/mL).
Results: 317 patients (60.3%) had chronic liver disease and 185 patients (35.2%) had liver cirrhosis. Most common cause of chronic liver disease was chronic hepatitis B in 185 patients (35.2%). HCC was diagnosed in 131 patients (24.9%). BCLC stage was stage 0 in 6 patients (4.6%), stage A in 64 patients (48.9%), stage B in 32 patients (24.4%), stage C in 29 patients (22.1%).
The AUROCs for the diagnosis of HCC of serum AFP level, AFP-L3 fraction, and PIVKA level were 0.772, 0.801, and 0.829, respectively. Diagnostic accuracy did not differ among these markers (all P > 0.05). The optimal cutoff values of serum AFP level, AFP-L3 fraction, and serum PIVKA-II levels were 4.0 ng/mL, 5.7%, and 35.0 mAU/mL, respectively. The AUROC of AFP-L3 level was 0.816. It was significantly higher than AUROC of serum AFP level (P < 0.001), while it did not differ with AUROCs of AFP-L3 fraction (P = 0.210) and serum PIVKA-II level (P = 0.682). The optimal cutoff value of AFP-L3 level was 0.26 ng/mL with sensitivity 72.5% and specificity 79.7%. The AUROC of ALPs score for the diagnosis of HCC was 0.877, which was significantly higher than those of serum AFP level (P < 0.001), AFP-L3 fraction (P < 0.001), PIVKA-II level (P = 0.005), and AFP-L3 level (P = 0.004). The optimal cutoff value of ALPs score was 5.05 with 82.4% of sensitivity and 82.8% of specificity. AUROCs for the diagnosis of early stage HCC of serum AFP level, AFP-L3 fraction, AFP-L3 level, PIVKA-II level, and ALP-II level were 0.689, 0.738, 0.754, 0.735, and 0.815, respectively. AUROC of ALPs score was significantly higher than those of serum AFP level (P < 0.001), AFP-L3 fraction (P = 0.034), and serum PIVKA-II level (P = 0.007), while there was a trend of higher AUROC of ALPs score than that of AFP-L3 level (P = 0.060). AUROC of ALPs score was significantly higher than that of serum AFP level (P < 0.001), while it did not differ with AFP-L3 fraction (P = 0.470) and serum PIVKA-II level (P = 0.748).
Conclusions: Diagnostic accuracy for the diagnosis of HCC was significantly improved with ALPs score, calculated using serum AFP level, AFP-L3 fraction, and serum PIVKA-II level. ALPs score was also very accurate for the diagnosis of early stage HCC. To confirm these results, validation study is needed.

THU465

The PNPLA3 G-allele is common in patients with HCC but does not affect tumor characteristics and tumor biology

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Background and Aims: The G-allele of the of patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) is an established risk factor for hepatic lipid accumulation and the development of advanced liver disease and HCC. This study explores a possible link between the *PNPLA3* G-allele and HCC tumor characteristics and biology.
Method: Patients referred for *PNPLA3* genotyping to the Hepatology Laboratory at the Medical University of Innsbruck were retrospectively assessed and included if the diagnosis HCC was made with multiphasic CT and/or dynamic contrast-enhanced MRI (n = 197). Tumor characteristics were assessed independently by two radiologists. An unselected *PNPLA3* genotyped cohort of cirrhotic patients without HCC (n = 1489) was used as a control group. Demographic, clinical and biochemical parameters were extracted from patient records.
Results: Of 197 (31 women) unselected HCC patients the G-allele prevalence was 70.6% (46.2% homozygous and 24.4% heterozygous). The allele frequency was not significantly different in an unselected cohort of cirrhotic patients (64.6%, p = 0.137) but far more frequent as in the general European population (allele frequency 0.228). At baseline (time of genotyping) age, median MELD scores and BMI did not differ between groups. When patients were grouped according to *PNPLA3* genotype no significant difference was observed in BCLC tumor stage, mRECIST defined tumor progression, tumor diameter and number, vascular tumor invasion and occurrence of extrahepatic metastasis. No association between *PNPLA3* and the combined endpoint death/liver transplantation was found. All before mentioned endpoints did also not differ between heterozygous and homozygous carriers.
Conclusion: Although G allele carriers in rs738409 of *PNPLA3* are known to be at increased risk of developing advanced fibrosis and HCC, no association between *PNPLA3* genotype and tumor characteristics, tumor biology or treatment response were found.

THU466

Long-term risk of HCC in persons with cirrhosis: national, population-based cohort study of 7,322 individuals

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Subgroup	Reference population, n (%)	Patients with cirrhosis, n (%)	Incident HCC, reference population, n (%)	Incident HCC, cirrhosis, n (%)	Incidence rate (95%CI) per 1000 person-years, reference population	Incidence rate (95%CI) per 1000 person-years in persons with cirrhosis	HR (95%CI)
All patients with cirrhosis	67382 (100)	7322 (100)	49 (0.07)	801 (10.9)	0.13 (0.09-0.17)	28.1 (26.21-30.10)	282 (189-420)
Viral hepatitis	22439 (33.3)	2511 (34.3)	8 (0.03)	398 (15.9)	0.07 (0.03-0.14)	43.55 (39.48-48-15)	580 (259-1299)
ALD	20988 (31.1)	2248 (30.7)	11 (0.05)	150 (6.7)	0.08 (0.05-0.15)	17.73 (15.11-20.80)	217 (96-492)
Metabolic disease	1119 (1.7)	125 (1.7)	2 (0.18)	18 (14.4)	0.30 (0.07-1.20)	34.67 (21.84-55.03)	Not possible to estimate
Autoimmune liver disease	5394 (8)	597 (8.2)	6 (0.11)	40 (6.7)	0.19 (0.09-0.43)	15.23 (11.17-20.77)	181 (44-751)
Other or NAFLD	17442 (25.9)	1841 (25.1)	22 (0.01)	195 (10.6)	0.20 (0.13-0.31)	25.09 (21.81-28.87)	159 (87-292)

Figure: (abstract: THU466)

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Background and Aims: Cirrhosis is the major risk factor for development of hepatocellular carcinoma (HCC). Most estimates on HCC risk derive from smaller cohorts and tertiary centres. We aimed to investigate the risk for incident HCC in individuals in Sweden with a new diagnosis of cirrhosis in a population-based study.
Method: We identified all individuals with a new diagnosis of cirrhosis in Sweden between 2001–2016 based on administrative coding during outpatient visits. We ascertained incident HCC until the end of 2016 by record linkage to national registers. Cirrhosis etiology was defined by pre-specified coding algorithms. Persons with multiple etiologies were excluded. Each person with cirrhosis was compared with up to ten general population reference individuals free of cirrhosis, matched by age, sex and living location. Cox regression was used to estimate hazard ratios (HR) with censoring for non-HCC related mortality.
Results: We identified 7 322 persons with cirrhosis, of which 2 511 (34.3%) had viral hepatitis, 2 248 (30.7%) alcohol-related liver disease (ALD), 125 (1.7%) metabolic disease other than NAFLD, 597 (8.2%) autoimmune liver disease, and 1 841 (25.1%) NAFLD or other causes of cirrhosis. These were compared to 67 382 reference individuals.
During 419 236 person-years of follow-up, there were 801 (11%) cases of HCC in patients with cirrhosis compared to 49 (0.07%) in the reference population. This corresponded to an HR of 282 (95%CI = 189–420). Risk estimates differed across etiologies of cirrhosis. HRs for HCC development compared to reference individuals together with incidence rates are presented in Table 1.
Conclusion: Patients with cirrhosis have a high risk of HCC development. The risk differs significantly across etiologies of cirrhosis. These data support an individualized approach in determining HCC risk in patients with cirrhosis.

THU467

Serum cytokeratin-19 fragments (CYFRA 21–1) for the prediction of overall survival in patients with hepatocellular carcinoma

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Background and Aims: Cytokeratin-19 (CK-19) is a cancer stem cell marker expressed by a subpopulation of hepatocellular carcinomas (HCCs) associated with tumor aggressiveness. It has been shown that serum levels of CK-19 fragments (CYFRA 21-1) correlate with the HCC expression of CK-19; hence we evaluated the prognostic value of serum CYFRA 21-1 compared to alpha-fetoprotein (AFP) and protein induced by vitamin-K absence-II (PIVKA-II) in patients with HCC.
Method: A total of 160 patients (28F/132M; age 65 [44–86] years) with a new diagnosis of HCC achieved between Nov-2012 and Jan-2018 were retrospectively analyzed. All patients had cirrhosis and the main underlying etiology was viral (118/160, 73.8%). Barcelona Clinic Liver Cancer (BCLC) staging system was adopted for patients classification and therapies allocation (18 stage 0, 77 A, 39 B, 23 C, 3 D). Radiological response to treatment was assessed by modified Response Evaluation Criteria in Solid Tumors (mRECIST). Serum

samples were collected at HCC diagnosis; CYFRA 21-1, AFP and PIVKA-II were measured on Lumipulse® G600 II (Fujirebio Inc, Japan).
Results: The median overall survival (OS) after HCC diagnosis was 35.1 (95%CI 27.1–35.1) months. At HCC diagnosis, median CYFRA 21–1, AFP and PIVKA-II levels were 1.3 (95%CI 1.2–1.5) ng/mL, 12.6 (95%CI 8.6–16.9) ng/mL and 199 (95%CI 146–316) mAU/mL, respectively. CYFRA-21 showed a poor correlation with BCLC staging (rs = 0.157, p = 0.048) and PIVKA-II (rs = 0.163, p = 0.039) but no correlation with AFP (rs = 0.072, p = 0.368). At univariate analysis, CYFRA 21-1 >2.7 ng/mL resulted a significant factor for poor prognosis (Log-rank test, p < 0.001). Multivariate Cox regression showed that CYFRA 21-1 >2.7 ng/mL (HR = 3.45, 95%CI 1.84–6.46), AFP > 20 ng/mL (HR = 2.20, 95%CI 1.24–3.90), PIVKA-II >200 mAU/mL (HR = 2.38, 95%CI 1.29–4.39), BCLC stage (HR = 1.61, 95%CI 1.20–2.16) and radiological response (HR = 0.21, 95%CI 0.08–0.55) were independent predictors of 3-year OS, while only CYFRA 21-1 >2.7 ng/mL (HR = 3.46, 95%CI 1.69–7.10), BCLC stage (HR = 2.00, 95%CI 1.36–2.95) and radiological response (HR = 0.09, 95%CI 0.01–0.72) were independent predictors of 1-year OS.
Conclusion: Among investigated biomarkers, CYFRA 21-1 resulted the strongest independent predictor of OS. The determination of baseline serum CYFRA 21-1 may be a useful prognostic factor.

THU468
Contrast-enhanced ultrasound using sonazoid in liver imaging reporting and data system category 3 and 4 observations on gadoxetate-enhanced magnetic resonance imaging

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Background and Aims: Contrast-enhanced ultrasound (CEUS) using perfluorobutane microbubble agent (Sonazoid) may have additional value for evaluating indeterminate focal liver lesions on gadoxetate-enhanced magnetic resonance imaging (MRI). We aimed to compare imaging features of gadoxetate-enhanced MRI and CEUS using Sonazoid in Liver Imaging Reporting and Data System (LI-RADS) v2018 category 3 (LR-3) and 4 observations, and to investigate the usefulness of CEUS to predict follow-up outcomes.
Method: We identified 136 LR-3 or LR-4 observations on gadoxetate-enhanced MRI which were subsequently evaluated with CEUS using Sonazoid in 131 patients (102 men and 29 women; mean age, 60.5 ± 9.3 years) with liver cirrhosis or chronic hepatitis B from 2013 to 2015. The presence of arterial phase hyperenhancement (MR-APHE), washout, and hepatobiliary phase (HBP) hypointensity on MRI, and the presence of APHE (CEUS-APHE) and Kupffer phase defect on CEUS were compared. In the subgroup of 53 observations which were not managed with ablation therapy, the follow-up outcomes were classified into high-risk group (pathologic proof of hepatocellular carcinoma, compact Lipiodol uptake after transarterial chemoembolization, or progression to LR-5 category within 6 months) and non-high-risk group. Logistic regression analysis was performed to identify imaging and clinical features associated with high-risk group.
Results: Thirteen (44.8%) of 29 observations without MR-APHE showed CEUS-APHE. Kupffer phase defect was demonstrated in 76 (81.7%) of 93 observations without washout and 6 (50.0%) of 12 observations without HBP hypointensity on MRI. In a subgroup analysis, 70.6% of high-risk group observations showed both CEUS-APHE and Kupffer phase defect at baseline, while 47.4% of non-high-risk group observations exhibited none of these features. Observations in the high-risk group tended to exhibit MR-APHE, washout, HBP hypointensity, CEUS-APHE, and Kupffer phase defect more frequently than those in the non-high-risk group. Multivariable analysis revealed that CEUS-APHE (OR, 8.38; 95% CI, 1.02–69.17; p = 0.048) and Kupffer phase defect (OR, 11.00; 95% CI, 1.52–79.86; p = 0.018) were independently associated with high-risk group.

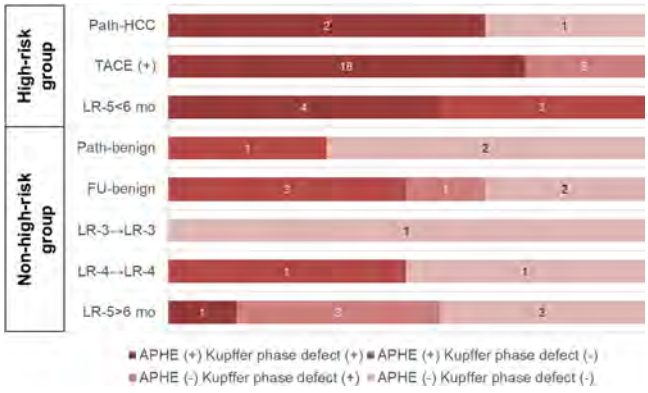

Figure: Baseline CEUS features according to follow-up outcomes.

Conclusion: The use of CEUS using Sonazoid can demonstrate additional imaging features, such as CEUS-APHE and Kupffer phase defect, in LR-3 or LR-4 observations on gadoxetate-enhanced MRI, which are independently associated with high-risk outcomes.

THU469
Active chronic hepatitis B increases the risk of liver metastasis - a retrospective observational study of 7,187 consecutive newly diagnosed colorectal cancer

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Background and Aims: Worldwide, colorectal cancer (CRC) is the fourth leading cause of cancer mortality and is increasing in medium to highly-developed countries especially in Asia and Europe. China has the highest number of new cases, accounting for about 28% of global CRC cases [1]. Asia also has a high burden of viral hepatitis B, many CRC patients in Asia also have chronic hepatitis B (CHB) infection. The effect of concomitant CHB infection on the risk of colorectal liver metastasis (CRLM) has not been definitively elucidated.
Method: We performed this retrospective, cross-sectional study of 7187 consecutive newly diagnosed CRC cases in three hospitals. All patients were hospitalized during the period between January 2010 and January 2016 and had pathological confirmation of their CRC. Patients were divided into different groups depending on the status of HBsAg ($HBsAg^+$ *vs.* $HBsAg^-$) or HBeAg ($HBeAg^+$ *vs.* $HBeAg^-$). The prevalence of synCRLM and baseline clinicopathological parameters were compared between these groups.
Results: The overall prevalence of synCRLM was 8.72% (627/7187) and was significantly higher in $HBsAg^+$ patients (43/368) than $HBsAg^-$ patients (576/6742) (11.68% *vs.* 8.54%, $P = 0.037$; χ^2 test; Table 1).
6074 patients had HBeAg test performed, and HBeAg positivity was noted in 1.14% patients (69/6074). In 368 $HBsAg^+$ patients, 365 patients also had HBeAg information, 19 $HBsAg^+/HBeAg^+$ patients and 40 $HBsAg^+/HBeAg^-$ patients showed elevated ALT, while only 2 of them were under the anti-HBV treatment. There were other 7 patients with normal ALT are under or had a history of anti-HBV treatment.
In further sub-group analysis, synCRLM was also more prevalent in $HBsAg^+/HBeAg^+$ patients (13/69) compared to $HBsAg^+/HBeAg^-$ patients (30/296) (18.84% *vs.* 10.14%, $P = 0.043$; χ^2 test). If 9 patients with anti-HBV treatment were excluded, synCRLM remained more prevalent in $HBsAg^+/HBeAg^+$ patients (13/67) compared to $HBsAg^+/HBeAg^-$ patients (30/289) (19.40% *vs.* 10.38%, $P = 0.032$; χ^2 test).

In univariate logistic regression analysis (Table 3), HBeAg positivity had the highest odds ratio (OR) [OR: 2.920, 95% confidence interval (CI): 1.558–5.371, $P = 0.001$] and was more than twice that of HBsAg positivity (OR: 1.417, 95% CI: 1.019–1.969, $P = 0.038$). In the subsequent multivariate analysis with other significant factors, HBeAg positivity was still the strongest predictor of synCRLM (OR: 2.473, 95% CI: 1.081–5.661, $P = 0.032$) (table 4), the OR of HBsAg positivity was 1.671 (95% CI: 1.060–2.633, $P = 0.027$) (table 5).
Conclusion: HBeAg positivity is a clinical risk factor for CRLM that can be readily identified and addressed. It is yet unclear if antiviral treatment can decrease the risk of liver metastasis in CRC patients, but future studies with carefully designed prospective trials will be needed to better define this.

THU470
Identification and etiology-dependent evaluation of diagnostic algorithms for early detection of hepatocellular carcinoma
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Background and Aims: Hepatocellular carcinoma (HCC) has limited treatment options when diagnosed late so early detection is crucial to reduce mortality. Multiple factors associated with cirrhosis, e.g. HBV, HCV or steatohepatitis are involved in the etiology of HCC and have an impact on disease course, diagnosis and therapy. Ultrasound is used for the surveillance of at-risk patients, but has limitations in the setting of NASH and severe liver disease. Alpha-fetoprotein (AFP) improves HCC detection but lacks sensitivity for small tumours. With the aim to improve early diagnosis of HCC in different at-risk populations, we identified biomarker panels with high sensitivity and specificity for early HCC and analysed their performance in context of liver disease etiology.
Method: Over 60 biomarkers were evaluated in a panel composed of 308 HCC cases including 125 early stages (BCLC 0 and A) and demographically matched 734 chronic liver disease controls (CLD) from a prospective multi-center study. Univariate and multivariate analysis were performed to distinguish early stage HCC and all HCC from CLD. Performance of the selected panels was compared to GALAD score (Gender, Age, AFP-L3, AFP, DCP). Impact of cirrhosis, HBV, HCV and non-viral etiology on clinical performance was investigated for each biomarker panel.
Results: In over 100.000 analyzed combinations AFP and PIVKA-II were the strongest features, but with limited sensitivity toward early stages. Addition of a 3rd biomarker: AFP-L3, IGFBP3, COMP or MMP3 together with gender and age further increased accuracy. Performance of the biomarkers was influenced by disease etiology: AFP showed robust performance in HBV, HCV and NASH/ASH; PIVKA-II had limited performance in ASH, while IGFBP3, MMP3 and COMP were affected by ASH/NASH. AFP-L3 performed well in HCV and NASH/ASH groups. Compared to other scores, GALAD showed superior robustness and clinical performance with AUC of 95% for all- and 90% for early HCC for viral- and non-viral etiologies. Performance in the cirrhosis cohort was 4% lower with AUC of 92% for all HCC and 87% for early HCC.
Conclusion: Analysis of over 100.000 biomarker combinations identified panels for early diagnosis of HCC with differential impact of etiology on their performance. None of the candidates showed sufficient performance as single marker and none of the identified scores was superior to GALAD. GALAD score showed robust diagnostic performance in both viral and non-viral etiologies and was only slightly affected by cirrhosis.

THU471
Optimisation and qualification of tumour mutational burden (TMB) by targeted next-generation sequencing (TNGS) as a clinically applicable biomarker in hepatocellular carcinoma (HCC)
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Background and Aims: Higher levels of somatic non-synonymous mutations associate with improved response and survival following immune-checkpoint inhibitors. In this pilot study, we aimed to optimise tNGS as a method to provide a reliable estimate of patients' TMB in HCC.
Method: Following macrodissection and DNA purification, 48 samples derived from an international biorepository (21 fresh-frozen [FF] and 27 formalin-fixed paraffin-embedded, [FFPE]) underwent tNGS by OncomineTM Tumour Mutation Load Assay (1.5 Megabase exome coverage) on an Ion S5TM sequencer. We performed uracil-DNA glycosylase (UDG) pre-treatment in a group of 11 FFPE samples to verify its effect on fixation-induced cytosine deamination. In total, 30/48 samples satisfied post-sequencing quality control and were included for clinicopathological correlation. We classified samples as high/low TMB based on median number of mutations/Mb (Mut/Mb), testing different minimum allele frequency (MAF) thresholds (≥ 0.05, ≥ 0.1 and ≥ 0.2) in relationship with clinicopathological features including Overall (OS) and Recurrence-Free survival (RFS).
Results: Eligible patients (n = 30) were mostly male, cirrhotic (84%) secondary to alcohol (48%) and Hepatitis C infection (45%). Median dominant tumour size was 4 cm with most patients being staged as TNM stage I-II (75%). Median OS was 12.3 months and median RFS was 12.1 months. FFPE samples displayed significantly higher TMB (median 958.39 vs 2.51 Mut/Mb, $p < 0.0001$), estimated deamination counts (median 1335.50 vs 0, $p < 0.0001$) and percentage C > T transition at CpG sites (median 60.3% vs 9.1%, $p = 0.002$) compared to FF. UDG-treated FFPE samples carried significantly lower TMB (median 4019.92 vs 353 Mut/Mb, $p = 0.041$), estimated deamination counts (median 6393.5 vs 328.5, $p = 0.041$) compared to untreated FFPE. Adjustment of MAF to 0.1 and 0.2 reduced deamination counts ($p < 0.05$), with a 0.2 threshold allowing for a reduction of TMB values within the interpretable range of <100 Mut/Mb in all samples. At a 0.2 MAF threshold with UDG treatment, the median number of non-synonymous mutations/Mb was 5.48 (range 1.68–16.07) and did not correlate with salient pathologic features of HCC including OS or RFS.
Conclusion: This pilot study highlights the challenges of TMB testing in archival tissue, where UDG pre-treatment and MAF adjustment to 0.2 allows for an improved assessment of TMB. Whilst tNGS on fresh

HCC samples appears the optimal source of somatic DNA, the low median TMB values observed here may limit the role of TMB as a predictive correlate of response to immunotherapy in HCC.

THU472

Integrated phenotyping of the anti-cancer immune response in HIV-associated hepatocellular carcinoma

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Background and Aims: HIV-seropositivity shortens survival in patients with hepatocellular carcinoma (HCC), a leading cause of mortality in people living with HIV (PLHIV) and hepatitis. Whether HIV pre-conditions cancer immune tolerance is unknown in HCC. This is a point of greater consequence given PLHIV are excluded from trials of immune checkpoint inhibitors. We intended to verify whether HIV status influences anti-tumour immunity by evaluating the functional characteristics of the T-cell infiltrate in tumour, peri-tumoral tissue and background cirrhosis.

Method: From an international biorepository of 55 HIV-associated HCCs from 4 centres in Europe and North America, we evaluated the expression of programmed cell death ligands 1 and 2 (PD-L1/2) in tumour and immune cells at a 1% cut-off. We explored their relationship with functional characteristics of the T-cell infiltrate (cytotoxic, regulatory and helper T-cell function) in tumoral, peritumoral and cirrhotic tissue. Immuno-pathologic features were correlated with patients' characteristics including markers of HIV infection.

Results: Of the 55 patients, 41 (85%) were male and had a median age of 52 years (range 41–64). Hepatitis C virus co-infection was the leading risk factor for HCC (n = 46, 90%). Most patients were of Barcelona Clinic Liver Cancer (BCLC) stage 0/A (n = 40, 85%), Child-Pugh A (n = 44, 86%), had median alfa-fetoprotein (AFP) values of 11 ng/ml (range 2–6536), undetectable HIV viral load (n = 31, 84%), and a median blood CD4+ cell count of 428 cells/mm^3. Patients were treated with liver transplantation (n = 39, 71%) or resection (n = 12, 22%). We observed tumoral PD-L1 expression in 24/55 (52%) and PD-L2 expression in 13/55 (28%) patients respectively. PD-L1 was frequently co-immunoexpressed in CD4 + FoxP3+ (49.0 vs. 8.2 cells/mm^2, p = 0.002) and CD8 + PD-1+ (40.8 vs. 12.3 cells/mm^2, p = 0.016) in tumour-infiltrating lymphocytes (TILs). This was not the case in PD-L2. PD-L1$^+$ HCCs had higher CD4$^+$FoxP3$^+$ TIL density compared to PD-L1$^-$ tumours (40.8 vs. 12.3 cells/mm^2, p = 0.014). PD ligands expression, CD4$^+$FoxP3$^+$ and CD8$^+$PD-1$^+$ cell density were independent of parameters reflective of HIV infection severity including peripheral blood CD4$^+$ count and HIV viral load. Peripheral CD4$^+$ counts positively correlated with CD4$^+$FoxP3$^-$ T-helper density in tumoral (r = 0.38, p = 0.032) and peri-tumoral cores (r = 0.45, p = 0.009), but not in surrounding cirrhosis. PD-L1 or PD-L2 expression was independent of patients' Child-Pugh class, AFP levels and did not predict for survival.

Conclusion: PD-L1 expression drives anti-tumour tolerogenesis in PLHIV with HCC, where prevalence of PD-L1 positivity (52%) is two-fold higher compared to historical HIV-negative controls (17%). Peripheral CD4$^+$ count is an appealing surrogate for effective T-helper infiltration in tumour and may guide the development of immunotherapy in HIV-associated HCC.

THU474

The burden of percutaneous liver biopsy use in hepatocellular carcinoma

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Background and Aims: The role of percutaneous liver biopsy (PLB) for the diagnostic workup for hepatocellular carcinoma (HCC) has become limited due to advancements in non-invasive diagnostic techniques. However, liver biopsy is still warranted under certain circumstances. We aimed to investigate the burden of PLB use for the diagnosis of HCC.

Method: We identified all the HCC related hospitalizations and PLB procedures using ICD 9-CM codes from the National Inpatient Sample (NIS) 2004 between 2014. Primary outcomes included the rate of LB procedures with secondary outcomes were in-patient mortality, length of stay (LOS), total hospitalization charges associated with these procedures. We also performed a univariate and multivariate regression analysis to account for confounding factors to predict the factors that can influence mortality and resource utilization in these patients.

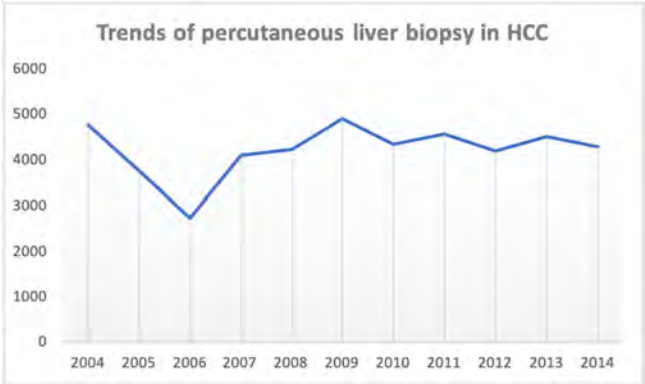

Figure: Number of percutaneous liver biopsy procedures performed through 2004 to 2014 in patients with hepatocellular carcinoma.

Results: A total of 390,393 HCC related hospitalizations with mean age 64 years and 31.74% of females were recorded. In total, 46,421 (11.89%) percutaneous liver biopsies were performed during hospitalizations between 2004 to 2014. A total of 38,687 (9.91%) of HCC related deaths occurred during the same admission, and 2,399 (5.1%) had PLB biopsies. Mean LOS was higher in patients who underwent

PLB 8.81 vs. 5.7 days, mean total hospitalization charges 69,840$ vs. 49,128$, mean total hospitalization cost 20,628$ vs. 14,449$. On univariate and multivariate regression analysis, black race (adj OR 1.26, p < 0.01), high charlson comorbidity index (adj OR 1.36, p < 0.01) transfusions (adj OR 1.41, p < 0.01, acute kidney injury (adj OR 2.5, p < 0.01) and sepsis (adj OR 3.2, p < 0.01) were found to be independent predictors of mortality in patients with HCC who underwent PLB. There was a significant downward trend noticed in the number of procedures performed in 2004 (4,777) as compared to 2014 (4,280).
Conclusion: Our study showed that a substantial number of patients with HCC still require PLB for the diagnostic workup, which adds to overall increased resource utilization. Large prospective studies are required to formulate validated diagnostic algorithm to further decrease the use of PLB in the diagnostic workup of HCC.

THU475

Epidemiological trends of hepatocellular carcinoma in patients with non-alcoholic fatty liver disease in Italy. On behalf of the ITA.LI.CA study group

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is projected to become the leading cause of hepatocellular carcinoma (HCC) in Western countries within 2025. The Italian Cancer Liver (ITA.LI.CA) database, that has collected over the last 20 years data of a huge western population of HCC patients, offers the ideal possibility to depict the epidemiological trends of NAFLD-associated HCC in the last years.
Method: We analysed 6,485 consecutive HCC patients diagnosed and enrolled from 2002 to 2017 in this multicenter Italian database. To describe epidemiological trends, the study period was divided in eight consecutive biennials (2002–2003 to 2016–2017). We analysed trends in liver disease severity, HCC stage and treatment strategies according to the HCC aetiologies.

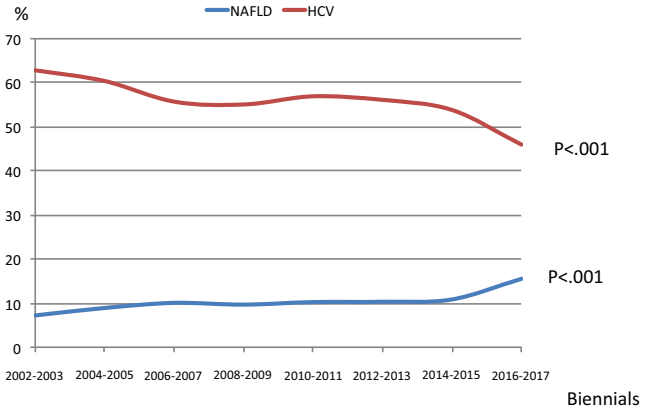

Figure 1: Epidemiological trends of NAFLD and HCV aetiologies in ITA.LI.CA patients with HCC, period 2002–2017.

Results: The proportion of NAFLD-HCC patients significantly increased in the study period from 7.19% in the first biennium, to 15.53% in the last (p < 0.001). Conversely, the proportion of hepatitis C related-HCC patients significantly decreased from 62.83% to 45.96% (p < 0.001). The proportion of hepatitis B related–HCC similarly decreased from 18.94% to 12.20% (p < 0.001), with a sharp decrease the overall of viral aetiology (p < 0.001). The proportion of HCC related to alcohol abuse remained stable around 16% (p = 0.183). Cirrhosis was present in about 75% of NAFLD-HCC patients, in contrast to the near totality of other HCC patients (p < 0.001). In addition, the proportion of cirrhosis in NAFLD-HCC patients slightly decreased from 86.67% in the first biennium to 74.7% in the last (p = 0.03). NAFLD-HCC patients showed less often a clinically significant portal hypertension and an early tumor stage, but these differences did not impact in their potential for radical therapies and overall survival (median survival 42 vs. 44 months in NAFLD vs other HCC patients, p = 0.77). Moreover, considering the different treatments and the ITA.LI.CA staging subgroups, no differences in overall survival were observed between NAFLD and other HCC patients.
Conclusion: The proportion of NAFLD-HCC in Italy has significantly increased from 2002 to 2017, with a progressive reduction of the association with cirrhosis (absent in about 1 out of 4 NAFLD-HCC patients). The outcome of NAFLD-HCC patients does not differ from that of the other HCC cases.

THU476

Circulating microRNA-21 and microRNA-122: prognosis prediction and correlation with HIF-1alpha in hepatocellular carcinoma patients treated with transarterial chemoembolization

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Background and Aims: MiR-21 and miR-122 have been identified as promising circulating biomarkers in hepatocellular carcinoma (HCC). We aimed to evaluate the prognostic role of their determination in HCC patients treated with transarterial chemoembolization (TACE), a treatment that induces liver ischemia, and the link, if present, with an angiogenesis biomarker (HIF-1alpha).
Method: Whole blood levels of miR-21 and miR-122 were evaluated in 40 HCC patients, 18 cirrhotics and 10 healthy volunteers, with a second determination in HCC 4 weeks after treatment (at the time of the imaging control). The miRNA level before TACE and the miRNA ratio (miRNA after/before TACE) were evaluated as potential progression-free survival (PFS) predictors. The Spearman's rank correlation coefficient was used to correlate miRNAs with HIF-1alpha. MiRNA levels were evaluated with qRT-PCR and expressed as $2^{-\Delta\Delta Ct}$; an ELISA method was used to measure HIF-1alpha levels.
Results: Both miR-21 and miR-122 were detectable in the blood of HCC patients at significantly higher levels as compared to healthy controls, with no significant differences with cirrhotics. A trend towards a decline in miR-21 after TACE (p = 0.056) was observed; miR-122 levels, despite being higher after TACE, were not significantly different. MiR-122 was higher in HCC patients with underlying viral liver disease (p = 0.03). High miR-21 levels before TACE (> median value) predicted favorable radiological response (chi-squared = 4.8; p = 0.03). MiR-21 ratio and miR-122 before TACE proved to be prognostic predictors: patients with levels of miR-21 ratio and miR-122 below the respective cut-off had a longer PFS (p = 0.0001 and p = 0.009, respectively) (see Figure). MiR-21 ratio, miR-122 and radiological response (mRECIST), were independent predictors of PFS at the Cox multivariate analysis. Moreover, miR-21 ratio and miR-122 were able to sub-stratify patients with complete or partial response in two groups, at favorable or poor PFS. MiR-21, but not miR-122, positively correlated with HIF-1alpha both before (r = 0.34, p = 0.049) and after TACE (r = 0.42, p = 0.01).

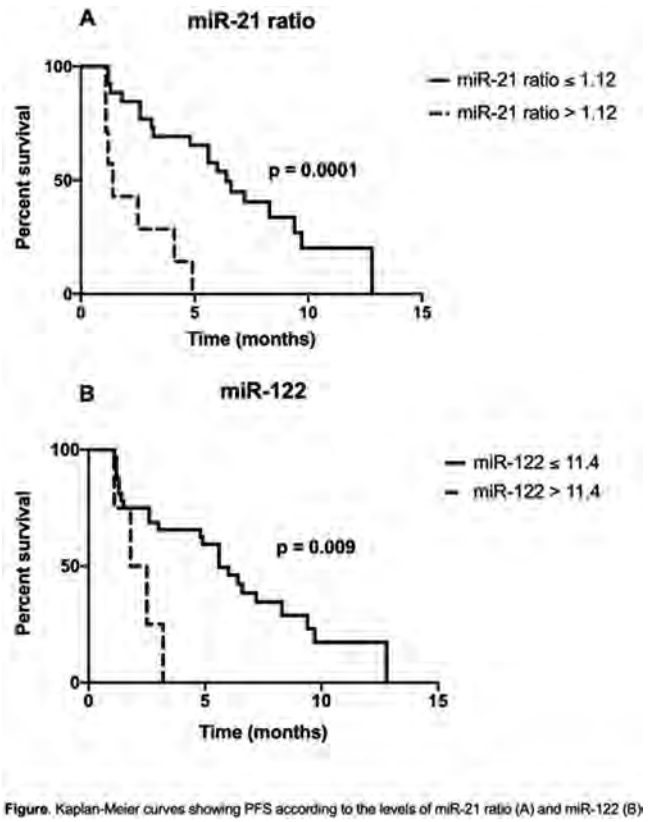

Figure. Kaplan-Meier curves showing PFS according to the levels of miR-21 ratio (A) and miR-122 (B)

Conclusion: MiR-21 and miR-122 are independent predictors of PFS in TACE-treated HCC patients and are able to identify, in patients with favorable radiological response, those with an early tumor progression after the treatment. The finding of a link between circulating miR-21 and HIF-1alpha in HCC indicate a potential role of miR-21 in angiogenesis.

THU477

Natural history of hepatobiliary-hypointense only nodules found at magnetic resonance imaging with Gd-EOB-DTPA: time-dependent effects of dimensional increase and diffusion weighted imaging alterations

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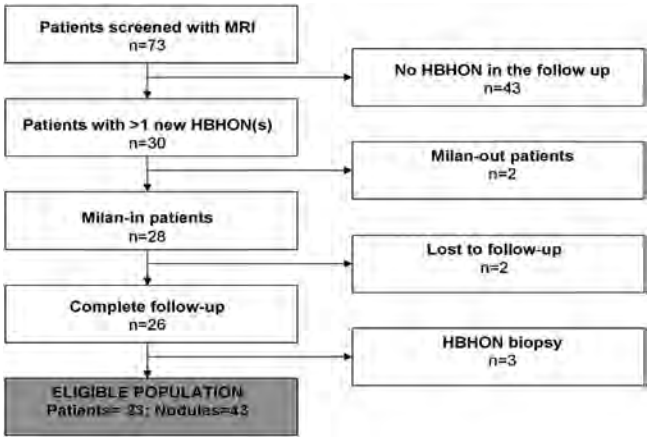
Background and Aims: HB hypointense-only nodules (HBHONs) are frequently found in cirrhotic patients performing magnetic resonance imaging. Some HBHONs can transform into overt hepatocellular carcinoma (HCC) overtime. Studies including only de novo HBHON (i.e. which were absent at previous MRI examinations) and using rigorous time-dependent analyses are still lacking.
Method: We evaluated consecutive patients performing MRI in the surveillance programs of HC due to a poor ultrasound visualization of the liver, analyzing only HBHONs appearing during the program (availability of a previous MRI performed no more than 6 months before the appearance of HBHONs to confirm that the nodule was not previously present). To better define the clinical repercussion of the detection of HBHONs, we excluded patients for which this finding would not have altered the clinical decision-making process (i.e patients with a concurrent Milan-out HCC at the time of the HBHON detection). The time-to-transformation (TTT) to HCC was correlated with the baseline characteristics of HBHON and with time-dependent modifications during the follow-up.
Results: Twenty-three patients and 43 nodules were included. After a median follow-up of 31.7 months, 19 nodules (45.2%) transformed into HCC. The 1-year and 2-year transformation rates were 11.9 and 31.0%, respectively. The median TTT was 17.8 months (95% CI 15.4–20.2). At the multivariable Cox regression with time-dependent covariates, the risk of evolution was 4-time increased after a dimensional increase >2 mm for the baseline and 5-time increased after the appearance of diffusion-weighted imaging (DWI) alterations. The median TTT shortened to 12.1 months (range 3.1–12.1) following the appearance of DWI alterations and to 4.9 months (range 3.1–34.3) after the first dimensional increase. Diameter of the nodule at its first appearance, previous/concurrent HCC, baseline T1 and T2 parameters were no related to an increased risk of transformation.



Conclusion: Examining only de novo HBHON, we provided for the first time relevant information about the natural history of these nodules. If confirmed in collaborative studies with larger populations, our data would pave the way for important policy-making decisions about the follow-up of HBHONs.

THU478

Comparison of prognostic models in predicting survival of patients with advanced hepatocellular carcinoma undergoing sorafenib treatment: a multicenter cohort study

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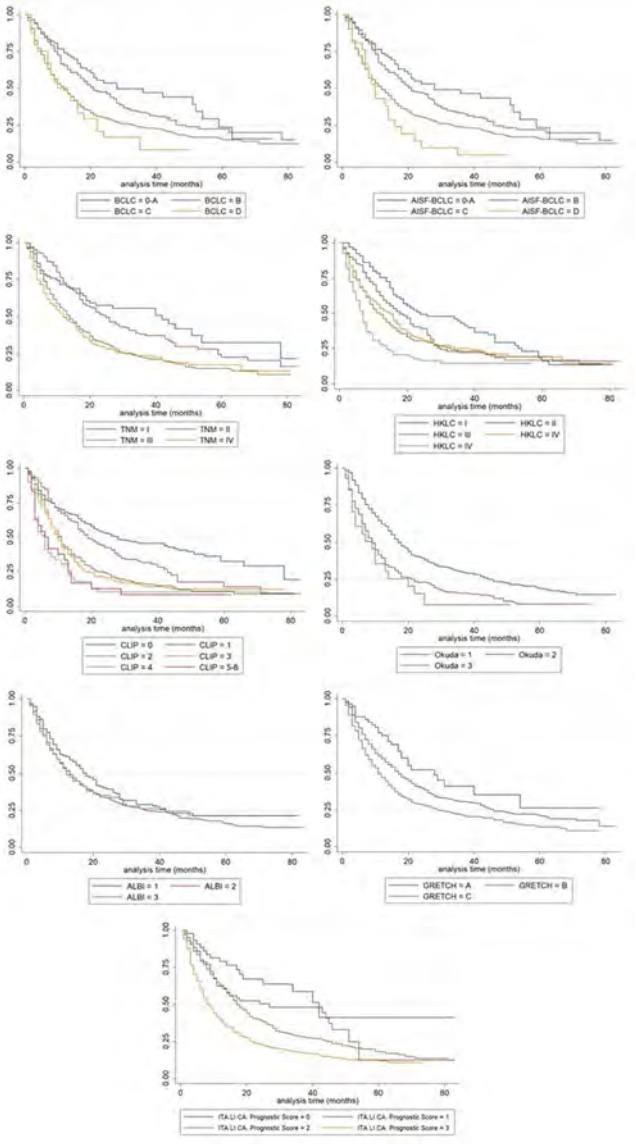
Background and Aims: Currently Sorafenib treatment is the gold standard therapy for patients with advanced hepatocellular carcinoma (HCC). To date, no widely validated scores are available to predict the overall survival of these patients. Thus, the aim of our study is to evaluate the accuracy of the current available prognostic scores for HCC to predict the overall survival of patients with advanced HCC treated with Sorafenib.
Method: We included all patients undergone Sorafenib treatment belonged to the prospective multicenter cohort of the Italian Liver Cancer (ITA.LI.CA.) database. We selected clinical data from the visit before treatment administration. Patients lost at follow-up were excluded. We assessed the performance of several prognostic scores [Barcelona Clinic Liver Cancer- BCLC, Italian Liver Association (AISF)-BCLC, TNM, Hong-Kong Liver Cancer- HKLC, Italian Liver Cancer score- CLIP, ITA.LI.CA. Prognostic score, Okuda score, Albumin-Bilirubin (ALBI) score, GRETCH score] through a univariate Cox regression model evaluating the C-index (Harrell's C) and the Akaike Information Criterion (AIC) of each prognostic score. A high C-index and a low AIC were indicator of good accuracy of the score.

Results: One-thousand and one-hundred and twenty-nine (1129) patients were included. The mean age of the patients was 61.6 years. A total of 80.8% of the patients enrolled were male. Seven-hundred and eighty-nine patients died during a median follow-up period of 15 months. The median period of Sorafenib administration was 4 months. During the follow-up 63.1% of the patients experienced a HCC progression. All the prognostic scores were able to independently predict the overall survival ($p < 0.001$) at univariate analysis, except for ALBI score ($p = 0.152$). The CLIP score yielded the higher accuracy (C-index: 0.608, AIC: 6565) followed by the ITA.LI.CA. prognostic score (C-index:0.594, AIC:8569) and the Okuda score (C-index 0.579, AIC 7257) among the scores evaluated.



Conclusion: The overall survival of patients included in ITA.LI.CA. database undergoing Sorafenib treatment is slightly higher than that reported in the current literature. To date, the CLIP score and the ITA.LI.CA. Prognostic score showed the highest accuracy in predicting the overall survival of these patients, although it remains poor. Further studies are needed to investigate the prognostic role of other clinical variables.

THU479

Prognostic and diagnostic role of angiogenesis biomarkers in hepatocellular carcinoma treated with chemoembolization

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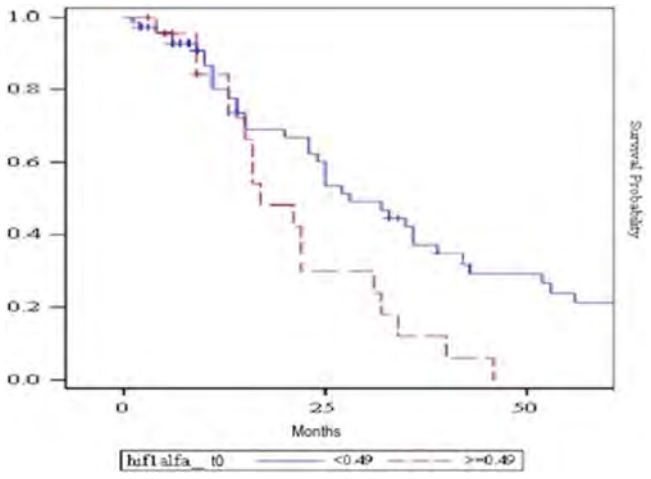
Background and Aims: Hepatocellular carcinoma (HCC) is the most common primary liver cancer, a tumor characterized by almost equal incidence and mortality, due to late diagnosis, insufficient and inadequate availability of therapies and with complex mechanisms of development and progression. Neo-angiogenesis plays an important role in HCC, to such an extent that it is considered as a possible therapy-target. We aimed to analyze the prognostic role of circulating VEGF-A and HIF-1α in patients treated by chemoembolization (TACE), the most used treatment for HCC whose mechanism of activity is, at least in part, based on its ischemia-inducing activity.
Method: We selected 163 consecutive patients classified as BCLC A/B treated by TACE and measured the two angiogenesis biomarkers concentration in sera and plasma from blood samples by ELISA tests before chemoembolization (t0) and after 4 weeks (t1) from the treatment. At t1 the patients' response to the treatment was assessed by CT scanning and mRECIST criteria. Statistics was applied as appropriate.
Results: Significant correlations between VEGF-A and the key tumoral and clinical features were documented [BCLC ($p = 0.009$), number of lesions ($p = 0.0001$) and complications ($p < 0.0001$)]. VEGF-A levels predicted treatment response by mRECIST criteria ($p = 0.014$). Patients with progressive disease (mRECIST PD) had significantly higher VEGF levels at t0 than those with complete response or disease control (mRECIST complete or partial response CR, PR, or stable disease, SD). On the other hand, HIF-1α t0 was significantly correlated only with lesions size ($p = 0.04$) and complications ($p = 0.002$). Finally, we analyzed the prognostic role of the two angiogenenesis biomarkers with a cut-off chosen on the basis of ROC curves. We found a statistically significant correlation ($p- = 0.01$) between HIF-1α t0 and survival, with a cut-off of 0.49 ng/mL. At Cox multivariate regression analysis, HIF-1α was confirmed as independent predictor of survival, together with Child-Pugh (p-value < 0.0001), etiology (p-value = 0.0028), lesion size (p-value = 0.004) and mRECIST (p-value = 0.0016).



Conclusion: Our findings suggest the potential use of VEGF-A and HIF-1α as additional prognostic criteria, possibly to be included in new staging systems, and support the everlasting search of molecules targeting angiogenesis to be used in the adjuvant or neo-adjuvant setting in HCC patients treated by TACE, an ischemia-inducing treatment.

THU480

Risk of hepatocellular carcinoma in hepatitis D co-infected patients compared to hepatitis B mono-infected patients: a systematic review and meta-analysis

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Background and Aims: Hepatitis D virus (HDV) infection is considered to cause the most severe viral hepatitis, with accelerated risks for cirrhosis and liver decompensation. However, whether it causes higher risk for hepatocellular carcinoma (HCC) is debated. We aimed therefore to evaluate the risk for HCC in patients with hepatitis B virus (HBV)/HDV co-infection compared to those with HBV mono-infection in a systematic review and meta-analysis.
Method: Ovid MEDLINE, PubMed, Embase and the Cochrane Library were systematically searched for studies reporting data on HCC risk among HBV/HDV co- infected patients and comparison group of HBV mono-infected patients, from inception until August 2019. Additionally, a comprehensive manual search was conducted. Only cohort studies with more than 20 patients in each group with minimum follow-up of 6 months were included. Two investigators independently extracted data, and data analysis was performed separately. Odds ratios were calculated and pooled together in a random-effects meta-analysis, generating pooled risk estimates with 95% confidence intervals (CI). Heterogeneity was assessed with I^2 and Q-test. Egger's test was used to assess publication bias and small-study effect.
Results: Of 3035 articles, 10 observational studies met inclusion criteria. Studies included 911 HBV/HDV co-infected patients with anti-HDV positivity and 14,694 with chronic HBV mono-infection. Overall, 11.96% (95% CI 10.01%–14.23%) of HBV/HDV co-infected patients developed HCC, whilst 3.41% (95% CI: 3.13%–3.72%) of HBV mono-infected developed HCC. The pooled analysis revealed an increased risk of HCC among patients with HBV/HDV co-infection (Effect size [ES] = 2.62, 95% CI 1.55–4.44, I^2 34.6%, P = 0.003). The association remained when excluding a study with high bias according to funnel plot visualization (ES = 2.76, 95% CI 1.77–4.30, I^2 29.5%, P < 0.001).

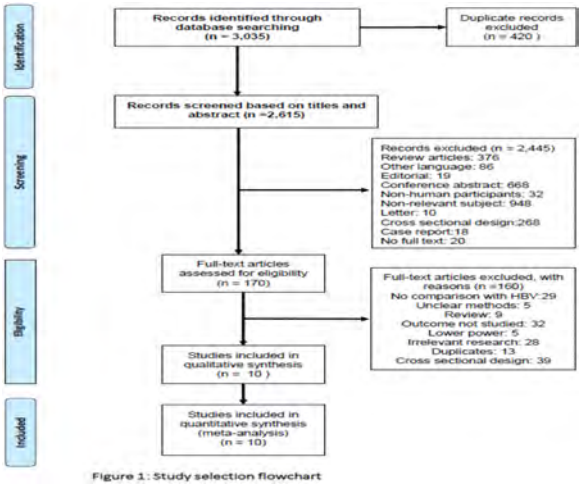

Figure 1: Study selection flowchart

Conclusion: These results suggest that HDV co-infection is associated with a 2.6 fold higher risk to develop HCC than HBV mono-infection, implying for a possible carcinogenic role of HDV. Better treatment options than currently available ones are needed, in order to cure HDV infection and minimize this risk.

THU481

The combination of EpCAM-positive circulating tumor cells and serum AFP/AFP-L3/DCP predicts outcome after curative resection of hepatocellular carcinoma

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Background and Aims: Early hepatocellular carcinoma (HCC) has a limited prognosis due to recurrence rates of more than 50% after liver resection. As reported earlier, EpCAM-positive circulating tumor cells (CTC) have a high predictive value for presence of micro-metastases and early HCC recurrence after resection, however, sensitivity remains low (22%) (von Felden, Schulze et al., Oncotarget 2017). The serum biomarker-triplet alpha-fetoprotein (AFP), lectin-reactive AFP (AFP-L3), and des-gamma-carboxy prothrombin (DCP) are well-known diagnostic and prognostic markers for HCC. The objective of this study was to evaluate a composite panel of CTC and the biomarker-triplet to identify patients with high risk of early recurrence after liver resection.
Method: We prospectively enrolled patients undergoing curative intended resection for HCC at a single institution between 2011 and 2015. Blood specimens were obtained prior to resection and processed with the CellSearchTM system, detecting EpCAM-positive CTC, and serum levels of AFP, AFP-L3, and DCP were measured with the µTASWako™ system. The primary endpoints were early recurrence within two years after resection, recurrence-free survival (RFS), and overall survival (OS).
Results: A total of 66 patients were prospectively enrolled (86% male, age 66 years, 84% early disease with one or two nodules). A positive test was defined as detection of CTC or any serum marker AFP, AFP-L3, or DCP above the local thresholds, and significantly associated with shorter RFS (7 vs. 20 month, p = 0.011) and OS (21 vs. not reached, p = 0.036). Multivariate regression analysis for early recurrence including the composite biomarkers, vascular invasion (V0 vs. V1/2), and status of resection margins (R0 vs. R1/2), revealed hazard ratios of 2.12 (95% confidence interval [95%-CI] 0.9–5.0, p = 0.084), 2.01 (95%-CI 0.92–4.4, p = 0.081), and 0.95 (95%-CI 0.3–3.0, p = 0.925), respectively. The sensitivity for the composite biomarkers to detect patients who will develop an early recurrence after surgery was 73%.
Conclusion: An easy to use blood-based composite test for detection of EpCAM-positive CTC and biomarkers AFP, AFP-L3, and DCP improved the sensitivity for the prediction of early recurrence, likely due to the presence of micro-metastasis at time of resection, and was able to discriminate outcome following curative-intended liver resection. Thus, the combination potentially identifies patients with more aggressive tumors who might benefit from adjuvant treatment.

THU482

Intratumoral EpCAM-positive cancer stem cell heterogeneity in patients with hepatocellular carcinoma and its impact on clinical outcome

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Background and Aims: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death. The genomic and histopathological heterogeneity among and within HCC tumours is of increasing interest. Dismal prognosis is often linked to invasiveness and metastatic potential of HCC harbouring cancer stem cell (CSC)-features (e.g. EpCAM-expression). However, knowledge on intratumoral EpCAM-expression and its impact on recurrence after curative-intended resection remains limited. This study aimed to investigate the spatial heterogeneity of EpCAM-expression within early HCC, and to identify its potential impact for the risk stratification of recurrence.
Method: We screened our biobank for suitable tissue from patients undergoing liver resection or transplantation between 2011 and 2017 to design a tissue microarray (TMA). Tumour specimens for TMA construction were sampled at multiple locations (n = 3–8). EpCAM-positivity was assessed for intensity and proportion to derive a score dividing three groups: EpCAM-negative (E−/−), heterogeneous-positive (E−/+), homogeneous-positive (E+/+). EpCAM score was correlated with the major clinical primary endpoints time to recurrence (TTR) and recurrence free survival (RFS).
Results: Overall we included 341 tumour spots from 75 patients (77% male, median age 66 years, liver cirrhosis 40.3%, liver fibrosis 34.3%). Aetiology consisted of alcoholic liver disease in 24.1%, NASH 16.5%, HBV 14.3%, HCV 17.6% and others 27.5%, representing a typical Western cohort. EpCAM score resulted in 32 E−/−, 36 E−/+, and 7 E+/+. E+/+ patients experienced significantly shorter TTR and RFS compared to E−/− and E−/+ patients (TTR 5 vs. 19 vs. 19 months, p = 0.03; RFS 5 vs. 14 vs. 15 months, p = 0.028, respectively). Interestingly, homogeneous EpCAM-positivity correlated with AFP levels >400 ng/ml, p = 0.034. A single spot had a positive predictive value for homogenous EpCAM-positivity of 45.7%, a negative predictive value of 100%, a specificity of 87.4% and a sensitivity of 100%.
Conclusion: Intratumoral EpCAM-expression has a high spatial heterogeneity. Only homogeneous positivity is significantly correlated with worse outcome, identifying patients in urgent need for adjuvant treatment. Additionally, our study demonstrates the importance of multiple sampling, which should be considered to identify patients for targeted treatment.

THU483

Quantitative magnetic resonance imaging predicts individual future liver performance after liver reception for cancer

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Background and Aims: The future liver performance (FLP) of an individual undergoing surgical liver resection to remove cancer is critical for their survival and recovery. We report the development and clinical testing of a novel magnetic resonance image (MRI) post-processing tool that combines quantitative multiparametric MRI with anatomical liver segmentation to estimate FLP. This is intended to inform the assessment of individualised operative risk and augment patient and surgeon decision making prior to liver resection.
Method: This software combines iron-corrected T1 (cT1) mapping, previously demonstrated to correlate with fibroinflammation and predict clinical outcomes in chronic liver disease, with a 3D U-net pipeline to automatically delineate the liver volume prior to defining Couinaud segments based on anatomical landmarks. Interactive removal of these segments, along with any interactively-defined virtual wedge resections, allows accurate estimation of the future liver remnant (FLR) volume, which when combined with quantitative cT1 mapping, provides a prediction of FLP, termed the "HepaT1ca score." The ability of this score to predict post-operative morbidity, length of stay and regenerative capacity was evaluated in a prospective clinical trial (ClinicalTrials.gov NCT03213314).
Results: Of the 143 patients recruited, 135 underwent liver resection. 84% of participants had liver metastases from colorectal cancer, with the remaining having primary liver cancer or other secondary cancers. 21% of participants had cT1 values above the upper limit of normal (795 ms) indicating increased risk of background liver disease. The HepaT1ca score showed a significant linear correlation with the modified Hyder-Pawlik score, an indicator of post-operative morbidity (adjusted $R^2 = 0.26$, $P < 0.001$), and liver regenerative performance (adjusted $R^2 = 0.46$, $P < 0.001$). Furthermore, in patients with an FLR below 90%, a high mean cT1 (>795 ms) was associated with a longer duration of hospital stay (median (IQR) of 6.5 (5.3–12) vs. 5 (4–7.1); P = 0.0053). cT1 also correlated with histological measures of inflammation and ballooning.

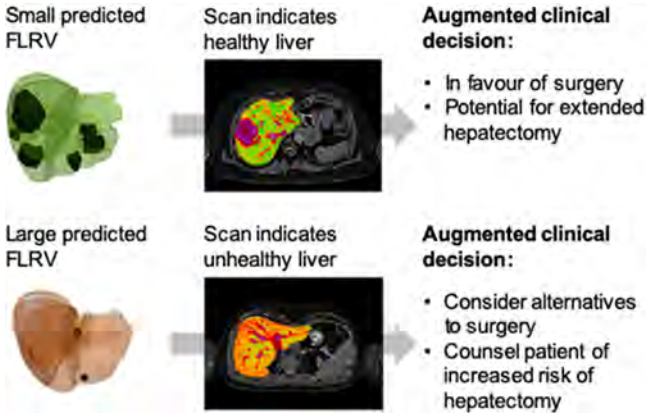

Figure: Concept diagram showing use of quantitative MRI in a clinical workflow highlighting exemplar case from the HepaT1ca study.

Conclusion: We demonstrate the utility of a non-invasive quantitative MRI approach for predicting post-operative liver performance. This has the potential to transform surgical decision-making and augment individualised risk assessment for patients undergoing liver resection for cancer.

THU484

Care pathway for patients with hepatocellular carcinoma in France in 2017: management overview, description of nurse coordinators' role and its impact

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Background and Aims: Nurse coordinators (NC) were implemented in several French units to manage care pathways of patients with hepatocellular carcinoma (HCC). Their missions, not clearly defined, may vary according to the hospital they work in. The aims of the study were to describe: 1) HCC management overview in France in 2017; 2) NC's role and impact on patients' management.
Method: A questionnaire-based survey collected online declarative data from 72 French units' physicians or NC between August and November 2018. It included a description of units' activity and NC's missions over 2017. We performed descriptive statistics and a bivariate correlation test according to NC's presence or not and delay in taking care of patients, length of stay (LOS) and diagnostic disclosure.
Results: Forty-two units (58%) replied, declaring a cumulative activity in 2017 of 9079 patients with HCC, including 4331 new cases (representing 40% of French annual incident cases).
More than 90% of these units performed hepatic surgery, percutaneous ablation, chemoembolization and systemic treatment. Conversely, radioembolization and liver transplantation were available only in 52% and 31% of units. Accessibility to clinical trials was proposed in 74% of them. Between 5 and 8 different specialists participated in multidisciplinary tumour board (MTB). NC actively participated in MTB in 24% of units. MTB occurred in less than 1 week and between 1 to 2 weeks in 25% and 58% of units, after the first contact with the patient.
For scheduled treatments, the expected LOS for chemoembolization, percutaneous ablation and radioembolization were 3.3, 2.2 and 3 days, respectively. Patients were hospitalised mostly in hepatology units (89%), less in digestive surgery (28%) or oncology (18%). Among these 42 units, 13 (31%), including 11 university hospitals, had 1 or 2 NC (10 and 3 units respectively). NC's main missions were providing information to patients (100%), monitoring side effects (85%), psychological support, intra and extra-hospital coordination (77%), organisation of treatments and monitoring (70%). NC's presence was associated in bivariate analysis with the number of patients treated per unit ($p < 0.1$). There was no difference in terms of delay in taking care or LOS in units. Conversely, there was a correlation between nurse's presence and a more comprehensive diagnosis disclosure according to the national cancer recommendations ($p < 0.05$).
Conclusion: Patients with HCC have a complex and heterogeneous care pathway. These declarative data show no difference in terms of delay in taking care or LOS in units with or without NC. However, their presence seems to be associated with a more comprehensive diagnostic disclosure. This pilot study is a first step to assess NC implication's impact on patients' management. A second study will analyse objective patients' cases data analysis.

THU485

Predicting survival after hepatocellular carcinoma resection using deep-learning on histological slides

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Background and Aims: The development of computational pathology and artificial intelligence promises to improve and standardize histological analyses, and may facilitate the extraction of "hidden" morphological features of potential clinical relevance. In this study, we used two deep-learning algorithms based on digitized histological slides, to build models for predicting the survival of patients with hepatocellular carcinoma (HCC) treated by surgical resection.
Method: Two independent series of patients were investigated: a discovery set (Henri Mondor Hospital, number of patients = 194, total of 390 whole image digitized slides (WSI)) used to develop our algorithms with cross-validation and an independent validation set (TCGA, number of patients = 328, total of 342 WSI).
The WSI were first divided into small squares, called "tiles", and features were extracted from these tiles with a pretrained convolutional neural network during the preprocessing step. During model development, the tiles were fed into the networks architectures. The first deep-learning based algorithm (designated as "SCHMOWDER") uses an attention mechanism on tumoral areas annotated by a pathologist while the second does not require human expertise.
Results: In the discovery set, c-indexes for survival prediction of SCHMOWDER and CHOWDER reached 0.78 and 0.75, respectively. Both models outperformed a composite score incorporating all baseline clinical, biological and pathological variables associated with survival. The prognostic value of the models were further valdiated in the TCGA dataset (c-indexes of 0.70 and 0.68 for SCHMOWDER and CHOWDER, respectively). As observed in the discovery series, both models had a higher discrimatory power than a score combining all relevant baseline variables associated with survival. Finally, pathological review showed that the tumoral areas most predictive of poor survival were characterized by vascular spaces, the macrotrabecular architectural pattern and a lack of immune infiltration.
Conclusion: Our study shows that artificial intelligence-based models using digitized histological slides predict overall survival after hepatocellular carcinoma resection more accurately than classical clinical, biological and pathological features. The analysis of areas classified as "low-risk" and "high-risk" by our model provides insight into the biological features that underly tumor aggressiveness.

THU486

Deep learning for cost-effective accurate diagnosis of liver tumor based-on magnetic resonance imaging and clinical information: a retrospective study

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Background and Aims: Early-stage diagnosis and treatment can improve survivals of liver cancer patients. However, short of ideal cost-effective screening tools and high cost burden of contrast agents calls for a new diagnostic strategy, in which deep learning may play a significant role. We aimed to develop and verify deep-neural-network models for accurate diagnosis of liver tumors with cost-effectiveness by analyzing MR images and clinical information.
Method: We derived a primary cohort of 1210 patients with liver tumors from Hepatic Focal Lesions Database of Sir Run Run Shaw Hospital affiliated Zhejiang University with linked MRI and medical records (N = 31608 images). The diagnosis-classification models were developed using enhanced images, unenhanced images, text and laboratory test results to get seven-way classifiers, binary classifiers and three-way malignancy-classifiers (Model A-Model G). Models

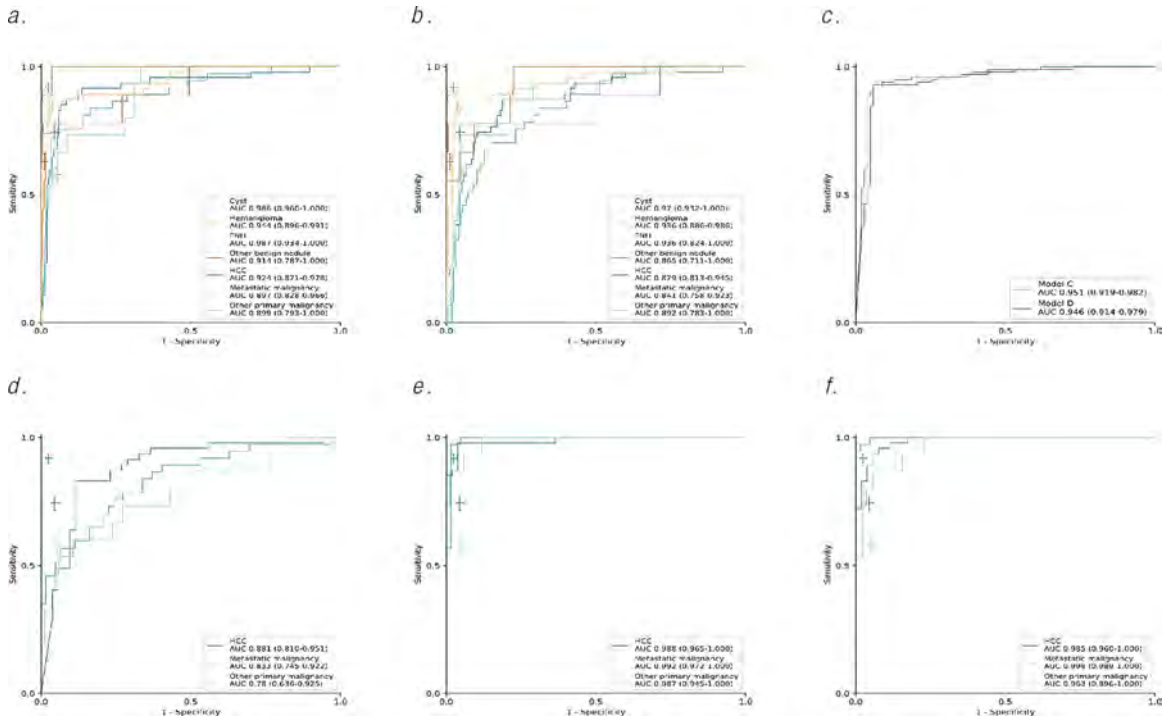

Figure: (abstract: THU486) **Performance of CNN models and radiologists in external validation set**. Receiver operating characteristic (ROC) curves for Model A-G. The crosses indicate the performance of average radiologists for each liver tumour category, the length of the cross represents the confidence Interval (CI).

were validated in an external independent extended cohort of 201 patients (N = 6816 images). Area under receiver operating characteristic (ROC) curve (AUC) were compared across different models. We also compared sensitivity and specificity compared with that of three experienced radiologists.

Results: Deep learning achieved competitive performance on par with experienced radiologists on seven-way classifier. Binary classifier using un-enhanced images achieved diagnostic performance similar to that using enhanced images (0.94 [95% CI 0·91–0·97] vs 0.95 [0.92–0.98], p = 0.66). New network combining unenhanced images with clinical data greatly improved the performance of classification for malignancy (AUCs of 0.98(0.96–1.00) for hepatocellular carcinoma, 0.99 (0.98–1.00) for metastatic tumors and 0.96 (0.89–1.00) for other primary malignancy). The agreement with pathology was 93.9%. These models mined diagnostic information in unenhanced images and clinical data by deep-neural-network, which were different with previous method that utilized enhanced images. The sensitivity and specificity of almost every category in these models reached the same high level compared to the consensus of experienced radiologists.

Conclusion: The current study is unprecedented in terms of disease diversity and diagnostic performance in absence of contrast agents. Models were trained with data in a various acquisition condition and new approach effectively integrated multimodal data. These are suitable for practical environment. It is potentially valuable and practical for non-invasive accurate diagnosis of liver tumors with cost-effectiveness.

THU488

The risk of hepatocellular carcinoma recurrence following resection or ablation is dependent on underlying etiology

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Background and Aims: Recurrence of hepatocellular carcinoma (HCC) following resection or ablation is a major clinical problem. However, the influence of underlying etiology on rates of HCC recurrence is not well understood. We sought to characterize the risk of HCC recurrence based on known risk factors following potentially curative therapies.

Method: From a large commercial US administrative claims database, we identified adults with a diagnosis of HCC accompanied by a potentially curative procedure (resection or ablation, but not transplantation) and no evidence of treatment failure within the next 90 days. All patients had ≥ 1 year of continuous insurance enrollment prior to cohort entry during which time no curative procedures occurred. Major HCC risk factors were identified at cohort entry including hepatitis B (HBV) and C (HCV), metabolic liver disease (i.e. non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, or metabolic syndrome), alcoholic liver disease (ALD), and cirrhosis/fibrosis. Patients were followed from end of curative procedure until the first of HCC recurrence, insurance enrolment end, or last date of data availability (March 2019). Absolute HCC recurrence rates per 100 person-years (PY) were calculated with exact 95% Poisson confidence intervals (CIs), and Cox regression was used to characterize risk of HCC recurrence according to etiology.

Results: Among 2,324 eligible patients, 108 had HBV, 276 had HCV, 560 had metabolic liver disease, 275 had ALD, and 640 had cirrhosis/fibrosis; 500 had more than one risk factor, and 1,149 had none. After a median follow up of 1.01 years (IQR: 0.46–2.36), absolute rates of HCC recurrence were highest among HCC patients with ALD, HCV, and cirrhosis/fibrosis. Among patients with HCV, 98% (270/276) had no evidence of DAA treatment at cohort entry. In multivariate analysis, significant independent risk factors for HCC recurrence included cirrhosis/fibrosis (hazard ratio [HR]: 1.35), ALD (HR 1.33), and HCV (HR 1.29). Metabolic liver disease and HBV were not associated with an increased risk of recurrence. Risks of recurrence were similar between antiviral-treated and untreated HBV patients (HR: 0.79 vs 0.78).

Table: Influence of Underlying Etiologies on HCC Recurrence Risk Following Resection or Ablation

Etiology	N Patients *	N Events*	Absolute Rate (95% CI)	Adjusted HR (95% CI)**	P-value
HBV	108	30	17.8 (12.0 – 25.5)	0.78 (0.54 – 1.13)	0.19
HCV	276	109	29.8 (24.5 – 36.0)	1.29 (1.04 – 1.60)	0.02
Alcoholic LVD	275	117	32.4 (26.8 – 38.9)	1.33 (1.08 – 1.64)	0.01
Metabolic Liver Disease	560	170	18.0 (15.4 – 20.9)	0.93 (0.78 – 1.10)	0.40
Cirrhosis/Fibrosis	640	258	26.4 (23.3 – 29.9)	1.35 (1.14 – 1.60)	<0.01

*Etiology categories are not mutually exclusive
** Mutually adjusted, including age group and sex

Figure: (abstract: THU488)

Conclusion: In this analysis of real-world data, HCC recurrence among patients treated with potentially curative procedures was common and differed by underlying HCC etiology. Cirrhosis, ALD, and untreated HCV infection were independently associated with increased recurrence risk. These results may have implications for surveillance of HCC recurrence in at-risk populations.

THU489

High subcutaneous tissue density correlates negatively with survival in patients with hepatocellular carcinoma

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Background and Aims: Prognostic stratification in patients with hepatocellular carcinoma (HCC) is based on parameters such as tumor burden, liver function and functional status of the patient. Body composition assessed by imaging techniques has been reported to contribute prognostic information in patients with various cancers. However, morphomics data in HCC is limited.
To assess the association between different body composition parameters measured on abdominal computed tomography (CT) scans and overall survival (OS) in two cohorts with newly diagnosed HCC in various stages.
Method: The area (cm^2) and density (Hounsfield Units) of skeletal muscle (SM), adipose tissue (subcutaneous (SAT), visceral (VAT) and intramuscular (IMAT)) were measured on CT scans at the level of the third lumbar vertebra in two cohorts of HCC patients (Bern, Switzerland n = 187 and Newcastle, United Kingdom n = 216). Univariate and multivariate Cox regressions analyses were used to assess the crude and adjusted association of body composition features with OS.
Results: In both cohorts, we found a significant variation of VAT density across Child Pugh classes and of SAT density among BCLC stages. Both body parameters tend to increase across Child Pugh classes and BCLC stages, respectively.
By univariate analysis, in both cohorts, only high SAT density (HR: 1.35; 1.12–1.62, p < 0.001 and 1.44; 1.27–1.63, p < 0.001, respectively) and high VAT density (HR: 1.38; 1.1–1.72, p = 0.005 and HR: 1.53; 1.3–1.81, p < 0.001, respectively) correlated negatively with survival. After model adjustment for potential baseline confounders (gender, age, diabetes, cirrhosis (yes/no), MELD score and BCLC stage) in a

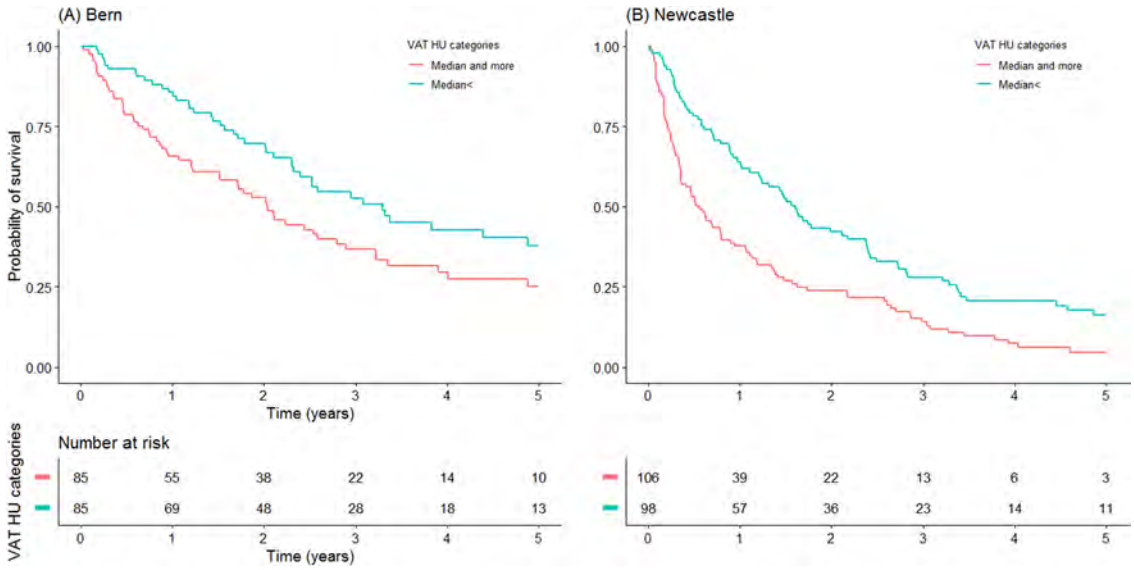

Figure 1: (abstract: THU489) Kaplan-Meier survival curves in groups of patients with low and high subcutaneous adipose tissue (SAT) density at the level of the third lumbar vertebra as determined by median - 97 HU for Bern cohort and -98 HU for Newcastle cohort. Log rank test in Bern, P = 0.042; in Newcastle, p = 0.003.

multivariate analysis, SAT density remained significantly associated with survival in both cohorts (Bern: HR: 1.27; 1.04–1.57, p = 0.022 and Newcastle: HR: 1.23; 1.03–1.48, p = 0.022) and VAT remained significantly associated with survival only in Bern cohort (HR: 1.31; 1.05–1.65, p = 0.019). Neither SM index nor SM density correlated with survival.
Conclusion: Based on two different HCC cohorts, our data show for the first time that a high SAT density assessed on CT scans correlates negatively with OS in HCC patients. Since HCC patients have CT scans for staging this new prognostic parameter can easily be obtained.

THU490
The protective role of urea-containing cream on sorafenib-associated hand-foot skin reaction in patients with hepatocellular carcinoma

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Background and Aims: Sorafenib has recommended as first line treatment in patients with advanced hepatocellular carcinoma (HCC) patients. Although sorafenib increase overall survival in patients with HCC, it has many side effects such as fatigue, diarrhea, vomitting, nausea, pruritus, depilation, Hand-Foot Skin Reaction (HFSR). Among them, HFRS is the most common side effect and it is main reason for dose de-escalation or discontinuation of sorafenib in patients with HCC. In this study, we aimed that investigate the role of urea cream in preventing the occurrence of HFRS or ameliorating severity of HFRS.
Method: Total 288 patients with HCC at 13 hospitals in Korea were randomly assigned from May 2016 to May 2018. Patients were treated with placebo cream and urea cream at the same time as starting the treatment of sorafenib. Patients were followed up for up to 12 weeks. HFSR, score for Hand-Foot Skin Reaction and Quality of Life (HF-QoL) questionnaire, and adverse event were assessed at 2, 4, 8, and 12 weeks.
Results: After exclusion of 41 patients, 247 patients with 117 patients in placebo control group and 130 patients in urea cream group were analyzed. Urea cream group showed lower cumulative incidence of any grade of HFRS (Log-rank, p = 0.247) and severe HFRS of 2 or more grade Log-rank, p = 0.394) without statistical significance. In the incidence by time point, development of severe HFRS of 2 or more grade were significant lower in urea cream group compared to placebo control group (13.8% vs. 23.9%, p = 0.042). Urea cream group showed significant improved score of HF-QoL questionnaire comparing with placebo control group (11.8 vs. 19.7, p = 0.014) at 12 weeks. There was no significant difference for overall survival (Log-rank, p = 0.748) between two groups. Tumor response were also not significantly different between two groups, which objective response rate was 6.2% in placebo control group and 6.0% in urea cream group (p = 0.957), and disease control rate was 44.3% in placebo control group and 42.0% in urea cream group (p = 0.741).

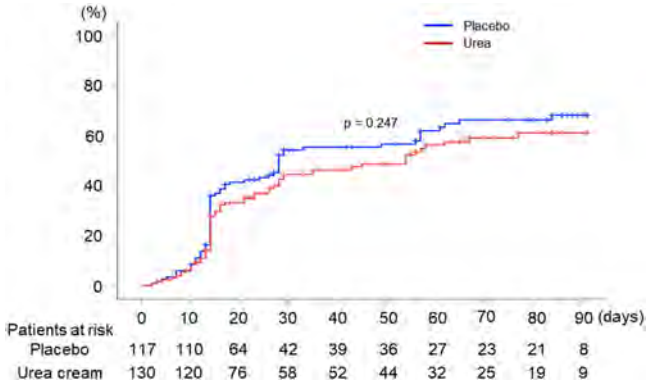

Figure: Cumulative incidence of any grade hand-foot skin reaction.

Conclusion: Treatment of urea cream showed decreased incidence of severe sorafenib-induced HFRS at 2 weeks and decreased tendency of development of HFRS in patients with HCC. Therefore, treatment of urea cream might be considered in patient that treated with sorafenib for HCC.

THU491
Applicability of the "six and twelve model" in patients with hepatocellular carcinoma treated with DEB-TACE

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Background and Aims: The effectiveness of transarterial chemoembolization (TACE) in hepatocellular carcinoma (HCC) depends on the selection of suitable patients. The "Six-and-Twelve" model [Wang Q et al, J Hepatol. 2019; 70(5): 893–903] has been developed and validated in an Asian cohort of ideal TACE candidates, and it distinguishes three groups with different overall survival (group 1, <6 points; group 2, 6–12; group 3, >12). This stratification based on the sum of number and size of tumors may impact in clinical practice and trials design. The score has been recently validated in a multicentric French cohort of patients treated with conventional TACE (n = 127) [Bourlière M et al. J Hepatol. 2019;71(5):1051–1052]. The aim of this study is to evaluate de usefulness of the "Six-and-Twelve" model in a cohort of HCC patients treated with DEB-TACE.
Method: observational retrospective study with consecutive HCC patients treated with DEB-TACE from October/2008 to October/2017; end of follow-up October 24th 2019. Exclusion criteria were Child-Pugh not available or ≥8, patients awaiting liver transplantation.
Results: 225 patients made up the study cohort: 187 men; 107 alcohol etiology, 70 HCV; Child A-5 n = 165, A-6 n = 43, B-7 n = 17; BCLC-0 n = 10, BCLC-A n = 102, BCLC-B n = 113. Median diameter of main nodule: 3.5 cm (IQR 2.5–4.8); median number of nodules 2 (IQR 1–3). Median overall survival (OS) was 27 months (95% CI 24.042–29.958), without differences in OS (25 months, 95% IC 20.734–29.266 vs 27 months, IC 95% 23.458–30.542, p = 0.586, respectively) between those with / without prior history of cirrhosis decompensation 34% (n = 77) and 66% (n = 148), respectively. OS was different between BCLC-0-A vs B: 32 vs 24 months, p = 0.004, and in Child-Pugh A5 compared to A6-B7: 30 vs 27 months, p = 0.005. The median value of

the "Six-and-Twelve" score was 6 (P_{25}-P_{75} 4.5–7.4). OS was different by stratifying through "Six-and-Twelve" model: group 1, n = 123, 32 months (95% CI 25.893–36.107) vs group 2, n = 101, 24 months (95% CI 19.576–28.424) vs group 3, n = 1, 27 months (p = 0.048).
Conclusion: The "Six-and-Twelve" model is a useful prognostic tool in patients with cirrhosis and HCC treated with DEB-TACE. As well as in the French cohort only few patients are included in the third group (score >12), therefore, the applicability of this model in our region is limited.

THU492
Application of acoustic radiation force impulse elastography in non-invasive diagnosis of focal nodular hyperplasia
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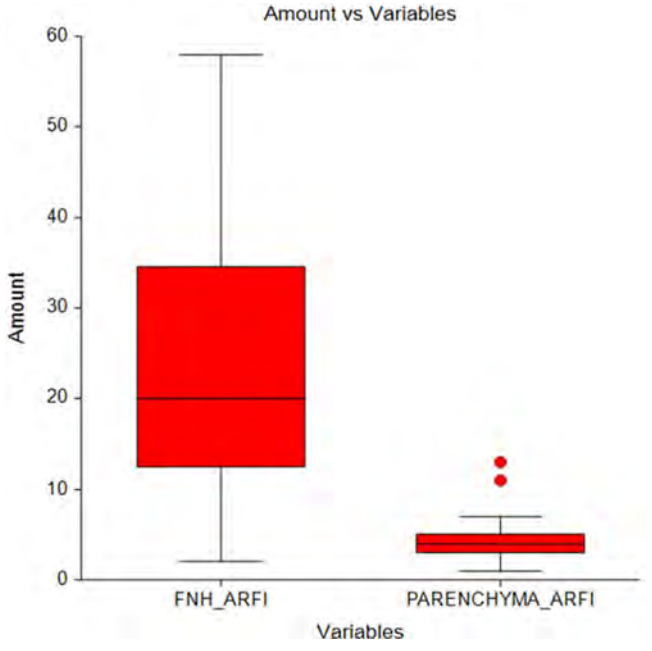
Background and Aims: Focal nodular hyperplasia (FNH) is a benign pseudotumoral lesion of the liver, result of a hyperplastic process due to limited alterations of the arterial vasculature. Its identification is usually incidental, but diagnosis is not always easy and may require multiple tests including invasive ones, such as liver biopsy. In last years the role of elastometry is emerging also for studying focal liver lesions. In two pilot studies on stiffness by acoustic radiation force impulse (ARFI) of focal lesions (Park, 2013, WJG; Zhang, 2013, HPDI), some FNH were included (4 and 14 pts respectively) and showed a higher stiffness than the other benign lesions. Our study aims to confirm, within a larger sample of patients, the diagnostic hypothesis that FNH has a higher stiffness than surrounding liver parenchyma.
Method: From November 2011 to November 2019, 61 patients with FNH coming to our Center underwent upper abdomen ultrasound with ARFI (results in kPa). Examinations were performed with Sonoline Antares (Siemens) with probe PHA 2–4.1 MHz and convex 2.5–5 MHz, from the same operator.



Results: Our population is composed of 46 women (75.4%) and 15 men (24.6%). The average age at observation is 38.9 + 9.02 y. Two patients (3.2%) were affected by Budd Chiari Syndrome (BCS) and only one (1.6%) by HCV cirrhosis. Other pts were not affected by any liver disease. 48 pts (78.6%) presented a single FNH vs 13 pts (21.4%) multinodular. The average diameter of the lesions was 49.5 + 22.4 mm. The diagnosis of FNH was made in 37 cases (60.6%) by radiological contrast imaging (34 MRI, 3 CT scan), in 4 cases (6.5%) by biopsy and in 20 cases (32.7%) by ultrasound for typical features. Among the 20 pts with ultrasound diagnosis there were 16 (26%) in which CT and MRI failed diagnosis.
The medium stiffness of FNH was 23.1 + 13.4 kpa vs 3.9 + 2 kpa of liver parenchyma (p.0001, Figure).
We calculated a ratio between FNH stiffness value and hepatic stiffness (ARFI ratio) for each patient: the average value was 6.8 + 3.7. In 59 pts (96.7%) ratio was >1.5. The only two cases with a lower value were two pts with liver disease: one with BCS and the cirrhotic. In both cases diagnosis was made by liver biopsy.
Conclusion: within our study FNH was showing significantly higher values than liver parenchyma in 96.7%, with an ARFI FNH/parenchyma ratio >1.5. The introduction of elastometric measurement in routine ultrasound can facilitate the diagnostic process and excessively expensive or invasive methods can be avoided.

THU493
Diagnostic and prognostic roles of circulating miRNA-223-3p in hepatitis B virus-related hepatocellular carcinoma
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Background and Aims: Circulating microRNAs (miRNAs) have been shown to dysregulate in many cancer types including hepatocellular carcinoma (HCC). The purpose of this study was to examine the potential diagnostic or prognostic roles of circulating miRNAs in patients with hepatitis B virus (HBV)-related HCC.
Method: Paired cancerous and adjacent non-cancerous liver tissue specimens of patients with HBV-related HCC were used as a discovery set for screening 800 miRNAs by a Nanostring quantitative assay. Differentially expressed miRNAs were then examined by SYBR green quantitative RT-PCR in a validation cohort of serum samples obtained from 70 patients with HBV-related HCC, 70 HBV patients without HCC and 50 healthy controls.
Results: The discovery set identified miR-223-3p, miR-199a-5p and miR-451a significantly lower expressed in cancerous tissues compared with non-cancerous tissues. In the validated cohort, circulating miR-223-3p levels were significantly lower in the HCC group compared with the other groups. The combined use of serum alpha-fetoprotein and miR-223-3p displayed high sensitivity for detecting early HCC (85%) and intermediate/advanced stage HCC (100%). Additionally, serum miR-223-3p had a negative correlation with tumor size and BCLC stage. On multivariate analysis, serum miR-223-3p was identified as an independent prognostic factor of overall survival in patients with HCC. In contrast, circulating miRNA-199a-5p and miR-451a did not show any clinical benefit for the diagnosis and prognostic prediction of HCC.
Conclusion: Our results demonstrated that miR-223-3p was differentially expressed in cancerous compared with paired adjacent non-cancerous tissues. In addition, circulating miRNA-223-3p could represent a novel diagnostic and prognostic marker for patients with HBV-related HCC.

THU494

Incidence of hepatotoxicity in patients with hepatocellular carcinoma on treatment with immune checkpoint inhibitors: impact on outcomes and tissue biomarker analysis

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Background and Aims: Factors leading to immune-checkpoint inhibitors (ICI)-related hepatotoxicity in hepatocellular carcinoma (HCC) remain poorly understood. We sought to assess: (i) incidence and predictors of immuno-related hepatitis during ICI, (ii) relationship between hepatitis grade and time to treatment failure (TTF), (iii) clinical and morpho-pathological factors linked to hepatitis.
Method: 58 patients with advanced/unresectable HCC received anti-programmed cell death protein 1 (PD-1)/PD ligand 1 (PD-L1) antibodies. Hepatitis was categorized according to National Cancer Institute's Common Terminology Criteria for Adverse Events. Tumor necrosis, intratumoral tertiary lymphoid structures (TILs), expression of CD34, Glutamine Synthase (GS), CD3 and CD79 were evaluated on 27 pretreatment tumor biopsies and were fitted into an Immune or an Exclusion class.
Results: 20 patients received anti-PD-1/PD-L1 antibodies alone and 38 in combination with anti- cytotoxic T-lymphocyte-associated protein 4 antibodies and/or tyrosine kinase inhibitors. After a median time of 0.9 months, 9 (15.5%) developed grade ≥ 3 hepatitis, which was not associated to any etiologic nor clinical parameter, except baseline ALT levels (p = 0.037). Steroids were administered in 3 patients and ICI were safely resumed in 6 out of 9 patients. No significant differences in TTF were seen with grade ≥ 3 hepatitis vs lower grades (3.25 vs 3.91 months, respectively; p = 0.81). Immunoreactivity to GS, absence of TILs, and necrosis were more frequent in patients developing grade ≥ 3 hepatitis (p = NS; Table).

Table: HCC morpho-phenotypical features according to the severity of ICI-related hepatitis

Tumor features	Grade ≥ 3 Hepatitis (N = 7)	Grade 0–2 Hepatitis (N = 20)	p
GRADE ≥ 3	2 (28%)	7 (35%)	1
NECROSIS	3 (42%)	3 (15%)	0.290
TILs	0	3 (15%)	0.545
VETC	5 (71%)	13/19 (68%)	1
EXCLUSION CLASS	7 (100%)	16 (80%)	1
IMMUNE CLASS	0	4 (20%)	0.545
AFP >400 ng/ml	2/5 (40%)	3/15 (20%)	0.545

Conclusion: Holding ICI and sporadically using steroids allow to safely reintroduce treatment with no detrimental effect on TTF. Though no predictor could be identified, preliminary analyses suggest that some biomarkers could be linked with onset of high-grade hepatitis.

THU495

External validation of the Toronto hepatocellular carcinoma risk index in Turkish cirrhotic patients

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Background and Aims: Toronto Hepatocellular Carcinoma Risk Index (THRI) is developed to stratify cirrhotic patients according to 10-year Hepatocellular Carcinoma (HCC) risk. We aimed to validate the performance of THRI in a large Turkish cohort.
Method: We retrospectively reviewed the database of 1287 cirrhotic patients followed-up in a 10-year period (February 2008–January 2018). All patients were stratified into three groups based on the THRI score as follows; low-risk: <120, intermediate risk: 120–240 and high risk: >240. Area under the curve (AUC) and optimal cut-off value of THRI was obtained from receiver operator curve (ROC). To reveal the parameters related with HCC development, logistic regression analysis was conducted. The cumulative incidences of HCC were calculated using Kaplan-Meier method, and the curves were compared using the log-rank test.
Results: Out of 403 enrolled patients, 57 developed HCC. The median THRI value was higher in HCC (+) group comparing to HCC (–) group (267 (70–366) vs 224 (36–366), p < 0.001). Out of 57 detected HCCs, 45 (78.9%) were high risk, 11 (19.3%) were intermediate risk and only one (1.8%) was low risk at the entry. The AUC of the THRI to predict HCC was 0.750(%95 CI 0.683–0.817, p < 0.001). The optimal cut-off value of THRI was 239.5, giving a sensitivity of 78.9% and specificity of 62.7%. As a result, THRI remained to be the only significant parameter that has an affect on HCC development (adjusted-OR:1.016 (95%CI 1.007–1.024), p < 0.001).
Conclusion: The present study validated the performance of THRI in cirrhotic patients to predict HCC risk, which can be considered as a tool for personalized surveillance.

THU496

Impact of baseline hepatitis B viremia and management on outcomes in advanced hepatocellular carcinoma and elevated alpha-fetoprotein: outcomes from REACH-2

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Background and Aims: REACH (NCT01140347) and REACH-2 (NCT02435433) were global, randomized, blinded, placebo (PL)-controlled phase 3 ramucirumab (RAM) trials in patients (pts) with

Table 1. Parameters associated with HCC development

	Univariate			M ultivariate		
	p value	OR	95%CI	p value	OR	95%CI
THRI	0.000*	1.015	1.009-1.020	0.000*	1.016	1.007-1.024
AST	0.190	1.003	0.999-1.007	0.879	0.998	0.969-1.027
ALT	0.555	1.002	0.996-1.007	0.858	0.998	0.973-1.023
ALB	0.007*	0.561	0.370-0.851	0.101	0.376	0.117-1.210
INR	0.107	2.939	0.793-10.892	0.160	15.247	0.342-679.386
T.bil	0.837	1.029	0.783-1.352	0.326	0.700	0.343-1.428
Cre	0.538	0.688	0.209-2.260	0.353	0.363	0.43-3.081
AFP	0.081*	1.045	0.995-1.098	0.669	1.028	0.905-1.169
FIB-4	0.002*	1.104	1.037-1.177	0.979	0.997	0.771-1.288
APRI	0.047*	1.132	1.001-1.281	0.827	1.085	0.523-2.247
BMI	0.327	1.033	0.968-1.103	0.196	1.053	0.973-1.140
MELD	0.225	1.085	0.951-1.237	0.144	0.746	0.504-1.105
CPS	0.283	1.117	0.913-1.367	0.932	0.973	0.520-1.822

AFP: Alpha-feto protein, ALT: Alanine transaminase, Alb: Albumin, AST: Aspartate transaminase, APRI: AST to Platelet Ratio Index, BMI: Body-mass index, Cre: Creatinine, CPS: Child-Pugh Score, FIB-4: Fibrosis-4 Score, MELD: Model for end-stage liver disease, INR: International normalized ratio, T.bil: Total bilirubin THRI: Toronto Hepatocellular carcinoma risk index

Figure: (abstract: THU495)

advanced hepatocellular carcinoma (HCC) following sorafenib. REACH-2 limited enrolment to pts with alpha-fetoprotein (AFP) ≥ 400 ng/mL, and met its primary overall survival (OS) endpoint, consistent with the prespecified REACH subgroup with baseline AFP ≥ 400 ng/mL. Analysis of pooled individual pt data from REACH (AFP ≥ 400 ng/mL) and REACH-2 showed improved OS with RAM versus (vs) PL for pts with hepatitis B virus (HBV) aetiology (7.7 vs 4.5 months [mos]; hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.55, 0.99). Here we investigate survival and liver function in REACH-2 pts with HBV aetiology tested for serum HBV DNA.

Method: Pts had advanced HCC, Child-Pugh A, ECOG PS 0/1, AFP ≥ 400 ng/mL, prior sorafenib treatment, and were randomized (2:1) to receive RAM 8 mg/kg or PL Q2W. Pretreatment serum HBV DNA was quantified by HBV-specific PCR (Roche) by a central lab. HBV DNA >15 IU/mL was detectable (HBV DNA+), <15 IU/mL was undetectable (HBV DNA-). OS in pooled treatment arms was evaluated by Kaplan-Meier method and Cox proportional hazards model. Liver function was assessed at baseline and before each cycle with the ALBI linear predictor. Outcomes were assessed by concomitant antiviral therapy. Adverse events (AEs) were graded by NCI-CTCAE v4.0.

Results: Of 107 REACH-2 pts with HBV aetiology, 106 had available PCR samples and were included in a pooled analysis (70 RAM and 36 PL pts). 48 pts were HBV DNA+ and 58 pts were HBV DNA-. HBV DNA+ pts had poorer median OS vs HBV DNA- pts (5.3 vs 10.1 mos, unstratified HR 1.45, 95% CI 0.93, 2.28). HBV DNA+ pts taking concomitant antiviral therapy (n = 36) had numerically improved OS compared with those without (n = 12) (5.8 vs 4.0 mos). No difference in OS was noted for HBV DNA- pts by antiviral therapy use (n = 39 antiviral; n = 19 no antiviral) (10.2 vs 9.7 mos for yes vs no antiviral). In pts taking antiviral therapy, regardless of HBV DNA serology, liver function was improved and liver injury/failure related AEs were less frequent.

Conclusion: Our data reinforce the use of antiviral therapy to improve outcomes in pts with advanced HBV-associated HCC and elevated AFP.

THU497

AFP is elevated more than 10 years before hepatocellular carcinoma development is detected: this observation leads to a practical risk stratification strategy

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Background and Aims: Screening patients with chronic liver disease for HCC is supported by all clinical guidelines. We aimed to develop a practical risk -stratification tool which would permit optimal use of resources within screening programs.

Method: Longitudinal discriminant analysis was applied to serial AFP changes to develop a risk model for the development of HCC. Internal and external validations were conducted.

Results: We analysed 3450 prospectively accrued patients from a single centre ('the primary cohort') with chronic liver disease (median follow-up = 8.83 years). 413 developed HCC (median follow-up = 6.60 years), within a rigorous HCC surveillance program (median HCC diameter at diagnosis = 1.8 cm). The model achieved an AUC of 78.4% and was able to correctly identify 74.3% of patients who would go on to develop HCC, and 72.9% of patients who would not.

Overall, 73.1% of patients were correctly classified. The model identifies high and low-risk groups (27.5 and 4.9 HCCs/1000 patient-years respectively). Similar results were found when the model was confined to patients with cirrhosis and in validation cohorts from Eastern and Western populations (Fig.).

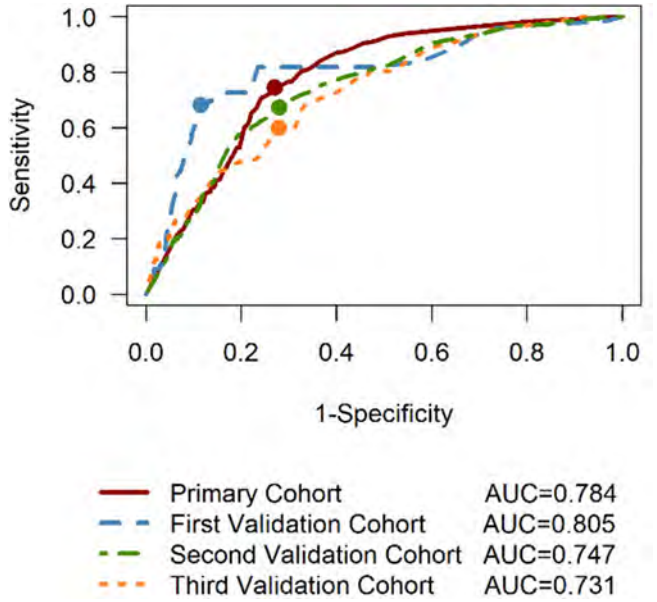

Figure: Receiver Operator Characteristic (ROC) curves for the primary and validation cohorts.

Conclusion: Our validated risk-stratification model assesses temporal changes in AFP and uses these to identify patients with chronic liver disease who are at high-risk of HCC development.

THU498

The prognostic and diagnostic significance of the neutrophil to lymphocyte ratio in hepatocellular carcinoma: a prospective controlled study

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Background and Aims: The neutrophil-lymphocyte ratio (NLR), a presumed measure of the balance between neutrophil-associated pro-tumor inflammation and lymphocyte-dependent anti-tumor immune function, has been suggested as a prognostic factor for patients with HCC. However, supporting studies have severe limitations including their retrospective nature, small numbers, lack of a relevant control group (chronic liver disease patients without HCC - CLD) and a rigorous statistical analysis that allows for potential confounding factors.
Method: A prospectively accrued cohort of 781 patients (493 HCC and 288 CLD) were followed up for more than 6 years. NLR levels between HCC and CLD patients were compared, and the effect of baseline NLR on overall survival amongst HCC patients was assessed via multivariable cox regression analysis.
Results: At baseline, there was no clinically significant difference in NLR between CLD and HCC patients. Amongst HCC patients, NLR levels closest to last visit/death were significantly higher compared to baseline. Multivariable cox regression analysis showed that NLR (along with AFP, bilirubin and BCLC stage) was an independent prognostic factor, even after adjustment for HCC stage.
Conclusion: In a prospectively accrued dataset, NLR was a significant independent factor influencing survival in HCC patients, hence offering an additional dimension in prognostic models.

THU499

Quantitative assessment of the impact of viral state on the rate of tumour progression in patients receiving sorafenib for advanced hepatocellular carcinoma

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Background and Aims: Although sorafenib remains the standard of care for patients with advanced hepatocellular carcinoma (aHCC), the tumour progression rate cannot be objectively assessed because of shorter survival amongst those who progress, so-called 'informative censoring'. We aimed to objectively quantify the rate of tumour progression and relate this figure to survival, both overall and in relation to viral status.
Method: Records from 502 patients receiving sorafenib for aHCC were analysed in a joint model that combines survival and change in tumour size, AFP and liver function over time. This permits an objective estimate of the rate of tumour burden growth and the impact of treatment on liver function in relation to viral status. The results were then tested for generalisability in a second analogous dataset of 588 patients.
Results: High tumour burden at baseline is associated with a significantly increased risk of death. The rate of increase in tumour burden was 12% (95% CI 10, 14) and the median doubling time (DT) was 665 days (95% CI 616, 735). The median survival amongst those who progressed was 237 days (95% CI 213, 281) compared to 449 days (95% CI 399-) among those who did not. The rate of tumour growth and serum AFP rise was significantly lower in HCV seropositive (as opposed to HBV or HCV negative patients) as was the rate of decline in liver function (Fig.). These results were replicated in the second dataset.

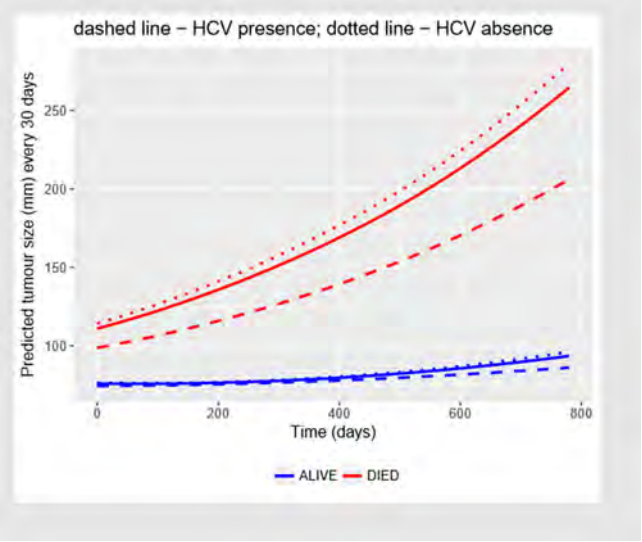

Figure: Change in tumour burden over time according to survival and viral status.

Conclusion: Our analysis suggests that sorafenib treatment benefits survival mainly by decreasing the tumour growth rate and improving liver function in patients with HCV.

THU500

Surveillance improves survival of intrahepatic cholangiocarcinoma arisen in liver cirrhosis

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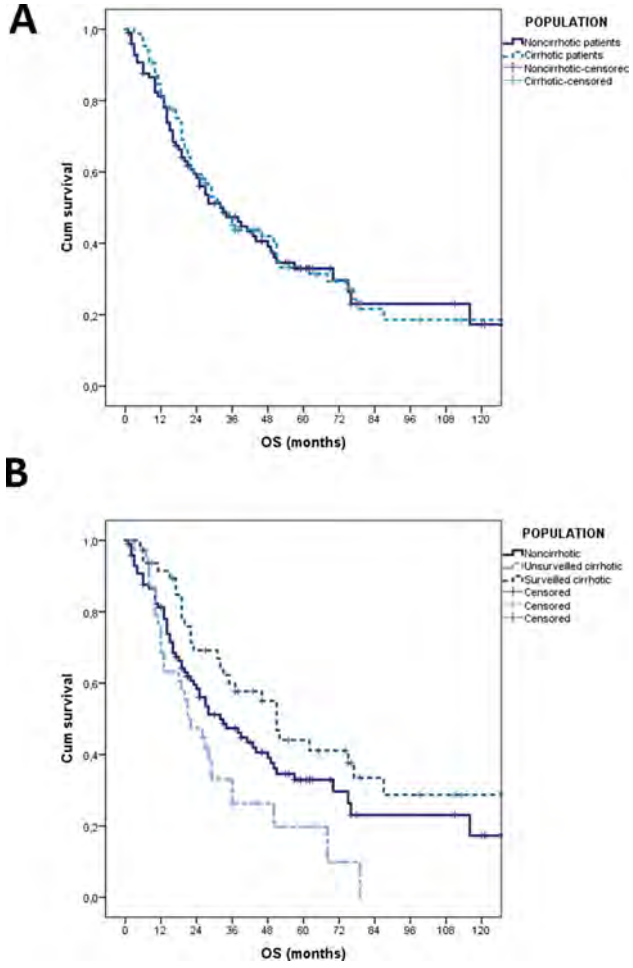
Background and Aims: Due to its poor survival, intrahepatic cholangiocarcinoma (iCCA) is held to be a much more aggressive cancer than hepatocellular carcinoma (HCC), but in most series patients were diagnosed when symptomatic. However, iCCA is now increasingly being discovered during the surveillance for HCC in cirrhosis. Whether earlier detection of iCCA in cirrhosis is associated nonetheless with a dismal prognosis or not is unknown.
Method: Multicenter retrospective study of consecutively enrolled patients with histological diagnosis of iCCA. Patients were statified into subgroups according to the absence/presence of cirrhosis. A propensity score matching was performed to reduce the potential iases deriving form different baseline characteristic. Cirrhotic patients were further stratified according to their surveillance status. The lead-time bias was estimated and effects of the surveillance on the survival were adjusted accordingly.



Results: Data from 185 patients were gathered. Eighty-five patients (46.2%) were cirrhotic. Liver cirrhosis was not related to a worse overall survival (33.0 vs 32.0 months, p = 0.800) even after the propensity score analysis (36.0 vs 43.0 months, p = 0.227). Amongst the cirrhotic population,47 (55.3%) patients had received a diagnosis of iCCA during a surveillance program. The two subgroup differed in the tumour dimensions at the diagnosis (30 vs 48 mm in surveilled and nonsurveilled patients, respectively). As a result, surveilled patients were more likely to be treated surgically (59.8 vs 28.9%, p = 0.003). OS was significantly different between surveilled and nonsurveilled patients (median overall survival 51.0 vs 21.0 months, p < 0.001). The benefit of surveillance was confirmed after correction for the lead-time bias (adjusted hazard ratio 0.464–95% confidence interval 0.271–0.796).
Conclusion: Cirrhotic patients have a different clinical presentation and disease course of iCCA according to their surveillance status, significantly influencing the chance of receiving curative surgery and therefore of obtaining satisfactory long-term outcomes. The discrepant results of previous studies evaluating the prognostic role of cirrhosis might be at least partly justified by this aspect. In our series, cirrhosis (compensated in the majority of cases) was not associated with worse outcomes, and therefore cirrhosis itself should not discourage neither surgical nor and locoregional and systemic treatments.

THU501

Refining the immune class of hepatocellular carcinoma

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Background and Aims: Immune checkpoint inhibitors have elicited unprecedented responses in several cancers, including hepatocellular carcinoma (HCC): nonetheless, only 15–20% of HCCs respond. A pre-existing inflamed tumour microenvironment (TME) may be essential for the activity of immunotherapy while specific oncogenic mechanisms have been reported to create a non-inflamed TME leading to ineffective clinical responses. Our study aims to characterize the HCC-TME and further define the Inflamed (described in Sia et al. Gastroenterology 2017) and non-Inflamed immune profiles of HCC.
Method: We assessed the presence of immune infiltration and tertiary lymphoid structures (TLS ≥ 5 foci, 10X) in haematoxylin eosin-stained slides, performed immuno-phenotyping (multiplex of CD8, PD1, and PDL1 and immunostaining for CTLA4, TIM3, LAG3 and TIGIT) and genomic analyses (RNA and whole-exome sequencing) in 240 HCCs encompassing the most common aetiologies (HCV = 90, HBV = 75, and non-infected = 75). T cell receptor sequencing (TCR-seq) was conducted in a subset of 40 samples.

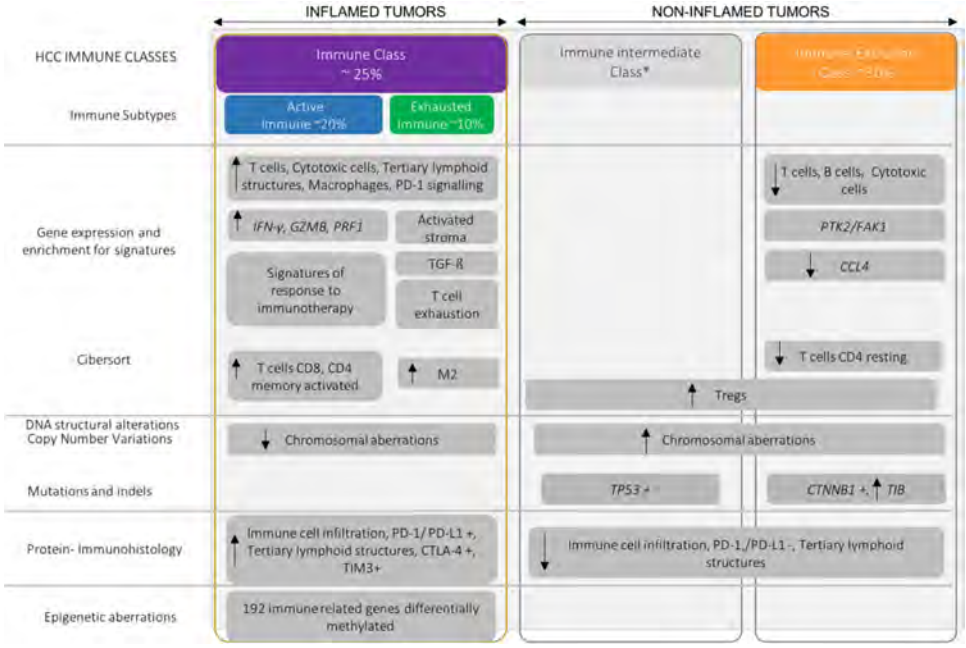

Figure 1: (abstract: THU501) Graphic representation of the three Immune classes and their molecular and histopathological features.

Results: High immune infiltration (15% of cohort) was associated with presence of TLS, higher intensity of CD8 and expression of immune checkpoints. LAG3 (29%), TIM3 (48%), CTLA4 (25%) and TIGIT (4%) showed no association with tumour mutational burden, aneuploidy or outcome. The recently described HCC Immune class or Inflamed profile was identified in 23% of patients, with no differences across aetiologies. The Immune class was linked to higher immune infiltration, CTLA4 and TIM-3 positive cases and higher CD8 and PDL1 intensities ($p < 0.05$). Patients with CTNNB1 activation (called Excluded class, 29% of tumours) displayed lower intensities of CD8, PD-1 and PD-L1, enrichment of Tregs and lower frequency of T CD4 resting ($p < 0.05$). The rest of the cohort was classified as Intermediate class, with a higher frequency of TP53 mutations (50% vs 26%, $p < 0.005$). The Immune class carried a significantly lower burden of chromosomal aberrations (broad and focal) compared to the rest. TCR-seq confirmed a higher fraction of T cells in the Immune Active class suggesting a more diverse and rich T cell repertoire in these tumours. Finally, while there was no difference in the tumour mutational burden, the Excluded class contained higher number of indels compared to the Immune class (Figure 1).
Conclusion: The characterization of the immune-TME of HCC has unveiled the existence of Inflamed (Immune class) and "non-inflamed" profiles (Intermediate and Excluded classes). The non-inflamed profiles show lower immune infiltration accompanied by the presence of oncogenic mechanisms associated with resistance to immunotherapy (i.e. mutations in CTNNB1) and immune evasion (high aneuploidy and TP53 loss).

THU502
Synergistic effects of extracellular vesicle phenotyping and AFP in hepatobiliary cancer differentiation

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Background and Aims: Large extracellular vesicles (EVs) are cell-derived membrane vesicles that express the same surface antigens as their parental cells. To improve hepatobiliary cancer screening and differentiation, we investigated the feasibility of EV phenotyping in distinguishing biliary cancer (CCA and GbCa) from HCC and other cancer entities. Furthermore, we explored if combining the serum tumor marker AFP with EV populations increased the diagnostic benefit.
Method: The presence of $gp38^+$, $CD133^+$, $EpCAM^+$ and $CD44v6^+$ cells and their combination was confirmed in human CCA and HCC cell lines *in vitro* and in various organs of wild type C57Bl/6J mice *in vivo* by FACS. EVs from patients' sera were isolated by sequential ultracentrifugation at 2,000 and 20,000×g. To identify EV populations FACS was applied with AnnexinV (AnnV) serving as EV marker. In total, 106 biliary cancer, 67 HCC, 32 NSCLC, 20 CRC patients and 48 healthy subjects were enrolled in the study.
Results: i) CD133 and CD44v6 were differentially expressed in CCA and HCC cell lines, indicating their potential for differential diagnosis. ii) $gp38^+CD133^+$, $EpCAM^+gp38^+CD133^+$, $CD44^+$ and $CD44^+CD133^+$ cells were found in murine liver, gallbladder, lung and colon, confirming possible parental cell populations for EVs. iii) All four surface antigen combinations on EVs ($AnnV^+gp38^+CD133^+$,

AnnV$^+$EpCAM$^+$gp38$^+$CD133$^+$, AnnV$^+$CD44v6$^+$ and AnnV$^+$CD44v6$^+$ CD133$^+$) allowed a significant distinction of biliary cancer from HCC, NSCLC, CRC and healthy subjects. AUC values for biliary cancer vs. HCC ranged from 0.68 to 0.81. iv) When combining EV populations with the serum tumor marker AFP, diagnostic values could be improved. AnnV$^+$gp38$^+$CD133$^+$ and AnnV$^+$EpCAM$^+$gp38$^+$CD133$^+$ EVs achieved 100% sensitivity (sens) and positive predictive value (PPV) for biliary cancer vs. HCC, while AnnV$^+$CD44v6$^+$CD133$^+$ EVs reached 100% sens and negative predictive value (NPV), respectively, with 97% specificity (spec) and 98% PPV. Remarkably, together with AFP AnnV$^+$CD44v6$^+$ EVs achieved a perfect separation of biliary cancer from HCC with 100% sens, spec, PPV and NPV, respectively.

Conclusion: Our results provide evidence that AnnV$^+$gp38$^+$CD133$^+$, AnnV$^+$EpCAM$^+$gp38$^+$CD133$^+$, AnnV$^+$CD44v6$^+$ and AnnV$^+$CD44v6$^+$ CD133$^+$ EVs, especially in conjunction with AFP, serve as a clinically relevant screening biomarker for biliary cancer and might clearly distinguish it from HCC. Thus, this method represents a minimal-invasive, accurate liquid biopsy screening tool for early and differential detection of hepatobiliary cancers.

THU503

Cholangiocarcinoma miscoding in hepatobiliary centres

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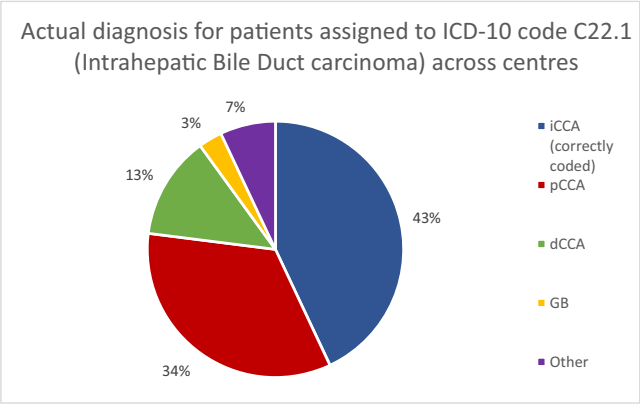
Background and Aims: Cholangiocarcinomas (CCA) are sub-divided into intrahepatic (iCCA) or extrahepatic (eCCA). eCCA are further subdivided into perihilar (pCCA) and distal (dCCA) cholangiocarcinoma. Current and previous versions of the WHO International Coding of Disease and Oncology (ICD, ICD-O) classifications, ICD-10 and ICD-O-3, have separate topography codes for iCCA and eCCA, but none for pCCA. Over recent decades, multiple studies have reported rising incidence rates of iCCA with declining rates of eCCA, without reference to pCCA. We hypothesised that the lack of a specific code for pCCA has led to errors in the coding of CCA, specifically with miscoding of pCCA as iCCA.

Method: Clinical and radiological notes of cases coded as hepatobiliary carcinoma using ICD-10 criteria (C22.1/Intrahepatic Bile Duct carcinoma, C24.0/Extrahepatic Bile Duct carcinoma, C23X/Malignant Neoplasm Gall Bladder, C22.0/Malignant Neoplasm Liver Cell Carcinoma) over a 2 year period (2015–2017), were reviewed by two independent clinicians at three independent UK regional HepatoPancreatoBiliary (HPB) centres. The final diagnosis was compared to the originally allocated ICD-10 code.



Results: Of 744 CCA cases reviewed, 119 were excluded due to insufficient data. Of the remaining 625 cases, 226 were coded as C22.1/iCCA. 98 (43%) of these were true iCCA and coded correctly, while 76 cases (34%) were actually pCCA. 92% all pCCA cases were incorrectly coded as iCCA.

Conclusion: CCA coding misclassification in UK HPB centres is common, particularly the miscoding of pCCA, which is extrahepatic and the commonest form of CCA, as iCCA. This may be contributing to apparent rising incidence rates of iCCA reported over recent decades. This confirms the importance of implementing separate topographical codes for iCCA, pCCA and dCCA in ICD-11 and future iterations of ICD-0.

THU504

Non-alcoholic steatohepatitis is a risk factor for intrahepatic cholangiocarcinoma and affects its long-time outcome: results from a multicenter international case-control study

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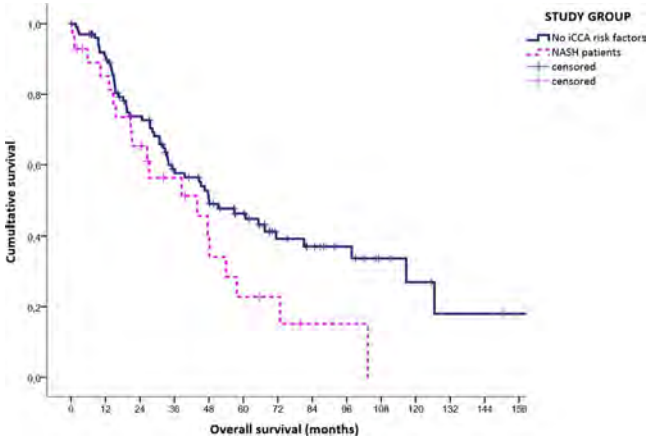
Background and Aims: The prevalence of intrahepatic cholangiocarcinoma (iCCA) is rising worldwide, for reasons not fully elucidated. The current epidemics of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) might be partly responsible for this trend. Last year we reported preliminary monocentric data providing a rationale for larger studies about the pathogenic and prognostic role of NASH in iCCA. We intended to validate our results in a larger multicenter international study, verifying whether NASH is over-represented in iCCA patients (primary aim) and whether it affects iCCA outcome (secondary aim).

Method: Case-control study comparing the prevalence of histology-confirmed NASH in the peritumoral liver of resected iCCA patients (cases) and pre-explant biopsies of liver donors (controls). Controls were matched 1:1 for age and sex. In the iCCA cohort, patients with no known risk-factors for iCCA were stratified according to the presence/absence of NASH. Correlates between NASH, tumor characteristics and overall survival (OS) were subsequently explored.



Results: Between 2004 and 2017, 181 ICC patients were resected in two European centers [Bologna (Italy) and Rennes(France)]. Among

the study population, 130 patients (71.8%) had no apparent risk factors for iCCA. In this group, the prevalence of NAFLD and NASH was 45.4% and 21.5%,respectively, compared to 38.5 and 6.2% in the matched liver donors (p = 0.343 and p < 0.001, respectively). The prevalence of NASH was similar in the two centers. Among patients without established risk factors for iCCA, main tumor size (HR 1.009, 95%CI 1.003–1.014, p = 0.003), multinodular disease (HR 1.767, 95%CI 1.092–2.861, p = 0.020) and NASH (HR 2.009, 95%CI 1.158–3.484, p = 0.013) were independent predictors of the OS at the multivariate Cox regression. The median OS was 43.9 vs 48.1 months, with the two survival curves significantly diverging after the first 36 months (Figure). Instead, NASH was not related to an earlier recurrence of iCCA (p = 0.748).

Conclusion: This multicenter study confirmed that NASH (but not NAFLD) acts as a risk factor for iCCA and affects its long-term outcome. The absence of significant differences in the time to recurrence and the late divergence of the OS curves suggest that difference in mortality is probably not attributable to a greater biological aggressiveness of NASH-related iCCA but rather to the liver- and nonliver-related complications of NASH.

THU505

Transcriptome profiling of liver biopsies before antiviral treatment start can predict HCC development 8.3 years before clinical diagnosis in chronic hepatitis B and C patients

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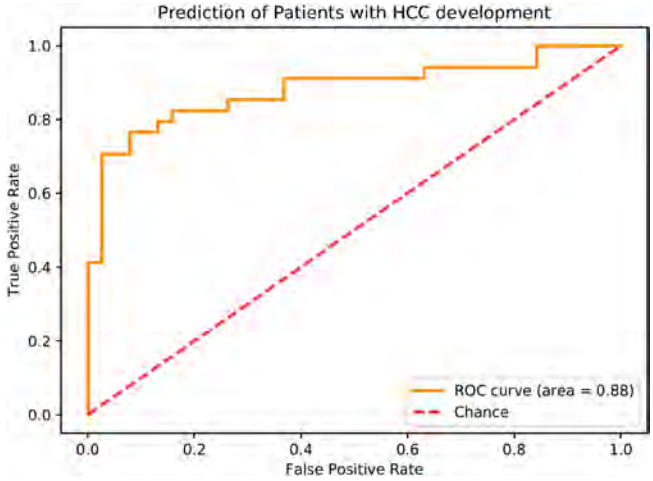
Background and Aims: An accurate prediction of Hepatocellular Carcinoma (HCC) development in Chronic Hepatitis B (CHB) and C (CHC) patients is currently impossible. In this study we explored pre-antiviral treatment liver transcriptome profiles of CHB and CHC patients with and without HCC development during long-term follow-up and investigated their potential to predict future HCC development.

Method: HCC developing cases (n = 34) were identified through retrospective chart review of all CHB and CHC patients with an available pre-antiviral treatment liver biopsy from 5 large Hepatology clinics. Cases were split in 4 subgroups based on infecting virus (HBV/HCV) and cirrhosis status (yes/no) at baseline liver biopsy. Each subgroup of cases was matched for different demographic (e.g. gender and age at biopsy) and clinical (e.g. cirrhosis at biopsy and infecting virus) factors to a group of controls without HCC development during an equal or longer follow-up time. RNA derived from baseline biopsies (total n = 72) was sequenced. Differentially Expressed Genes (DEG; FC >1.5 and q <0.2) were called in each subgroup and a random forest classifier was trained to predict HCC development.

Results: The total cohort consisted of 72 patients, of whom 34 developed a HCC at a median of 8.3 years after liver biopsy. Despite perfect matching for clinical and demographic characteristics, at least 452 DEG were found between cases and controls in each subgroup. Among the top 20 up- and down-regulated genes in each subgroup, 40–75% has previously been linked to oncogenesis, underlining the biological relevance. Ingenuity Pathway Analysis showed an enrichment for the "Wnt-bèta catenin signaling" pathway in the cirrhotic CHB group and the "molecular mechanisms of cancer" pathway in the non-cirrhotic CHC group. These results strongly suggest a genetic imprint for HCC development several years before clinical diagnosis. A random forest classifier tested with leave-one-out-cross-validation was able to predict HCC development with an accuracy of 84.7% (Figure 1), a Negative Predictive Value of 92.1% and a Positive Predictive Value of 75.8% based on the subgroup and baseline expression levels of 20 genes, of whom several have previously been linked to hepatocarcinogenesis.



Conclusion: Pre-antiviral treatment liver biopsies of chronic hepatitis B and C patients show a genetic imprint for future HCC development that allows to accurately predict HCC development 8.3 years before clinical diagnosis.

THU506

TERT mutated circulating tumor DNA is a useful biomarker and predicts prognosis in Danish HCC patients

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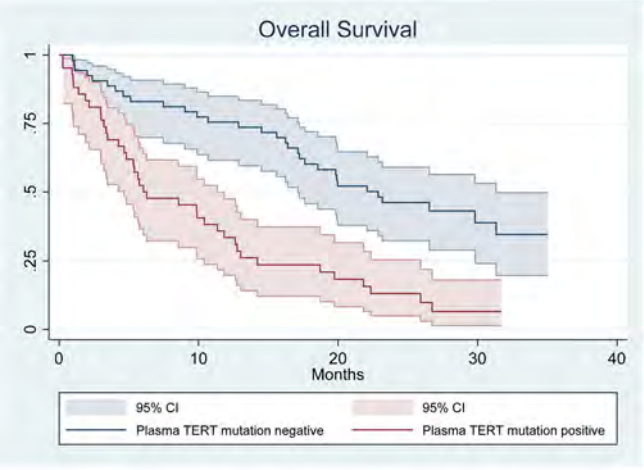
Background and Aims: No biomarker is able to diagnose hepatocellular carcinoma (HCC) with high sensitivity and specificity or provide clinically useful prognostic guidance. Circulating tumor DNA (ctDNA) with tumor-specific mutations is an attractive biomarker. The *Telomerase Reverse Transcriptase* (TERT) C228T promotor mutation is the most prevalent tumor-associated mutation in HCC.

The mutational landscape of HCC depends on the etiology of any underlying liver disease. The aims of this study is to evaluate TERT mutation in plasma as a prognostic marker and evaluate presence of TERT mutation in a Danish patient cohort primarily consisting of patients with alcoholic cirrhosis.

Method: We analyzed plasma DNA from Danish patients, 95 with HCC and 44 with liver cirrhosis without HCC for the TERT promotor mutation using droplet digital PCR. In 34 HCC cases we also analyzed DNA from the corresponding primary tumors, and calculated the concordance rates. We investigated the association between presence of TERT mutation in plasma and tumor DNA and survival.
Results: Plasma TERT mutation was detected in 42/95 HCC patients (44%), but in none of the non-HCC patients. Moreover, TERT mutation was detected in 23/34 tumor samples (68%). In HCC patients, TERT mutation was associated with increased mortality when detected in plasma ctDNA (HR 2.27, P = 0.005, adjusted for BCLC stage and sex), but not in tumor DNA (HR 1.39, P = 0.52, adjusted for BCLC stage and sex). For HCC patients with BCLC stage C, we observed a difference in median survival of 10.4 months depending on plasma TERT mutational status (p = 0.024).
Analysis of TERT mutations in plasma and tumor DNA from the same patient was concordant in 21/34 cases (62%; kappa value 0.31, P = 0.014), 11 being double-positive and 10 double-negative. In the 13 non-concordant cases, TERT mutation was found in tumor DNA from 12 patients (92%) but not in the corresponding plasma DNA.



Conclusion: Plasma TERT mutation was found in 44% of Danish HCC patients and was associated with increased mortality. Moreover, plasma TERT mutation was specific for HCC patients, not being identified in non-HCC cirrhotic patients. We suggest TERT C228T mutation in ctDNA as a promising biomarker in HCC for both diagnosis and prognosis.

THU507

Comparison of hepatocellular carcinoma between the current decade and the past - a study of 3,013 cases

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Background and Aims: Hepatocellular carcinoma (HCC) is a significant global problem for many decades. In view of changing disease patterns and advances in HCC diagnosis and therapy, our hypothesis is that there are significant differences in the clinical characteristics and treatment of HCC in the current decade compared to the past.

Method: Patients with HCC from 3 major tertiary hospitals in Singapore (Singapore General Hospital, Tan Tock Seng Hospital and National University Hospital System) were enrolled into a Research Electronic Data Capture (REDCap) database between 1980 and 2018. Clinical characteristics and treatment of HCC diagnosed in the current decade i.e. from 2008 were compared with those diagnosed before 2008. IRB approval for the study was obtained.
Results: There were 3,013 patients. Mean age of HCC diagnosis was significantly older in the current decade (68.6 vs 61.2 years, p < 0.001). Overall, majority were males (80.5%) and Chinese (84.6%). There were significantly more foreigners in the current decade (6.7% vs 4.3%, p < 0.007). Although the most common etiology remained as chronic hepatitis B (CHB) infection, the proportion due to CHB was significantly less in the current decade (46.6% vs 57.2%, p < 0.0001). Concurrently, cryptogenic/nonalcoholic steatohepatitis (NASH) has become significantly more important in the current decade (27.1% vs 18.6%, p < 0.0001). More patients received curative therapy in the current decade (43.7% vs 27.1%, p < 0.0001).
CHB is diminishing in lieu of cryptogenic/NASH as an etiology of HCC. This is in line with our nationwide hepatitis B vaccination program since 1985 coupled with the improved socioeconomic status of our population and ensuing increase in prevalence of NAFLD/NASH. The significant rise in the age of diagnosis of HCC in the current decade may be due to better treatment of CHB infection. There are more foreigners in the current decade due to the growth of Singapore as a regional medical hub. The proportion of patients who received curative therapy is significantly higher in the current decade, likely due to early diagnosis from more inclusive HCC surveillance programs together with advances in the diagnosis and therapy of HCC.
Conclusion: In this largest collection of 3,013 cases of HCC in Singapore accrued over more than 3 decades, patients are diagnosed at an older age and NASH is becoming more important as an aetiology of HCC in the current decade. It is heartening that more patients are amenable to curative therapy in the current decade.

THU508

Cholangiocarcinoma in England - a national study examining changes in incidence, diagnostic routes and overall survival

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Background and Aims: Cholangiocarcinoma (CCA) incidence rates have been rising internationally for several decades. The causes are unclear. It is not known if there have been changes to diagnostic routes, patterns of presentation or overall survival.
AMMF in partnership with the National Cancer Registration and Analysis Service (NCRAS) in Public Health England (PHE) calculated incidence and mortality rates for England during 2001–2017, the first national survival study 2001–2017, and Routes to Diagnosis (RTD) statistics (Elliss-Brookes *et al.* 2012) between 2006–2016.
Method: Age-standardised incidence and mortality rates, Kaplan-Meier overall survival (OS) estimates and the distribution by RtD for CCA (ICD-O-3: C22.1; C24.0; C24.8; C24.9; and C22 [excluding C22.1] with morphology code 8160) were determined using data from the PHE NCRAS population-based cancer registry.
Results: There were 29,653 CCAs diagnosed between 2001–2017, 51.6% were female, and the median age of diagnosis was 75 years (IQR 66–82).

The incidence rate increased on average by 0.8 per million per year from 2.9 per 100,000 in 2001 to 4.4 in 2017 whilst the mortality rate increased by 1.3 per million. Rates increased more rapidly in the most socio-economically deprived population, 1 per million for incidence and 1.5 per million for mortality.
Between 2001–2017, 1-year OS increased from 20% to 25%, and median survival from 7.1 to 9.5 months. The 5-year OS remained below 5%.
The RtD data showed that the proportion of patients diagnosed following an emergency presentation fell from 51% in 2006 to 47% in 2016.

Figure: Incidence, Mortality and Survival of Cholangiocarcinoma in England.

Conclusion: Incidence and mortality rates of CCA in England are increasing. The more pronounced increase in rates observed for the most deprived group is similar to findings from an NCRAS study of primary liver cancer (Konfortion *et al.* 2014), and are suggestive of an association between increased deprivation and increased exposure to known risk factors for CCA.
The median survival for CCA is poor, lower than that reported for primary liver cancer (Maluccio *et al.* 2017). Just under half of CCA patients present through an emergency route which previous studies have shown is associated with a worse clinical outcome (McPhail *et al.* 2013).
These findings emphasize the need to clarify risk factors and develop tools for earlier diagnosis, improving outcomes in this patient group in line with the NHS Long Term Plan.

THU509

Reduced incidence of hepatobiliary cancers in helicobacter pylori infected persons in a population-based cohort study

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Background and Aims: *Helicobacter pylori* (*H. pylori*) infection is known to be involved in intestinal cancer carcinogenesis. As regards hepatobiliary cancers, *H. pylori* DNA/RNA has been isolated from liver tissue from patients with hepatobiliary cancer, but no direct association has been established.
This large cohort study investigated *H. pylori* infection and its association with the incidence of hepatobiliary cancers. The cohort's appropriateness for the purpose was gauged by its ability to identify the established risk relation to gastric cancer.

Method: This historical study was performed in the Central Denmark Region. Patients were included from the primary health care after being tested for *H. pylori* infection with a urea breath test (UBT) and followed for a median of 4.6 years. Patients' diagnoses, country of birth, and gender were obtained from national Danish administrative registries. Cox regression was used to compare incidences of hepatobiliary and gastric cancer between *H. pylori* positive and *H. pylori* negative persons, adjusting for confounding variables.
Results: A total of 53,633 persons were included and 10,553 were tested positive for *H. pylori*. We found a markedly lower incidence of hepatobiliary cancers (equally for both hepatocellular- and cholangiocarcinoma) in *H. pylori* positive persons; HR = 0.27 (95% CI 0.11–0.68). The increased incidence of gastric cancer was confirmed (HR = 1.99 (95% CI 1.35–2.94)).
Conclusion: This cross-sectional study, which is the first, large historical cohort study on this topic, showed that *H. pylori* infection may protect against hepatobiliary cancer. However, our data offer no mechanistic explanation of this protective effect or whether *H. pylori* infection is merely a proxy for other protective factors.

THU510

Prognostication of hepatocellular carcinoma under sorafenib: external validation of the PROSASH-II model

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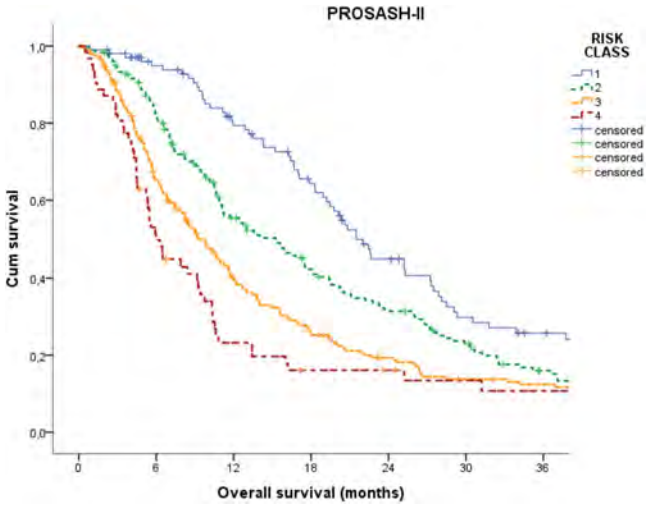
Background and Aims: Prognostic classifications for patients treated with sorafenib for hepatocellular carcinoma (HCC) can be an useful tool to facilitate stratification in trials and inform clinical decision making. Very recently, Labeur and colleagues developed the PROSASH-II model, which performed better than other existing models in predicting the overall survival (OS) of sorafenib-treated patients. As this study included a 4-center training set and a single-center validation, further validation in multicenter cohorts are needed to understand the full potential of the PROSASH-II model. Aim of our study was to verify the stratification performance of the PROSASH-II and comparing with other existing prognostic models.
Method: We analyzed a large retrospective-prospective database gathering the clinical data of 552 patients from 7 Italian centres, who were prescribed with sorafenib between 2008 (date of licence in Italy) and 2017. The PROSASH –II score was calculated as proposed by its creators [(–0.0337 × albumin in g/l) + (0.315 × Ln(bilirubin in µmol/l) + (0.295 × macrovascular invasion, where 0 = No and 1 = Yes) + (0.181 × extrahepatic spread, where 0 = No and 1 = Yes) + (0.0336 × Largest tumour size in cm) + (0.0703 × Ln(AFP U/L)). It was subsequently categorized as follows: ≤-0.0760 (risk group 1), > –0.0760 to ≤ 0.355 (risk group 2), >0.355 to ≤ 0.858 (risk group 3) and >0.858 (risk group 4). The performance of the PROSASH-II was compared with those of BCLC, ALBI, HAP score and SAP score.
Results: The PROSASH-II stratification significantly discriminated patients, with a median OS of 21.5 months for risk group 1, 15.3 months for risk group 2, 9.3 months for risk group 3, and 5.9 months for risk group 4. Using risk group 1 as a reference, the hazard ratio was 1.52, 2.04, and 3.0 for risk groups 2,3, and 4, respectively. PROSASH-II

showed improved discrimination (C-index 0.61) compared with existing prognostic scores (C-index ≤ 0.57).



Conclusion: Our results validate the PROSASH-II as an effective prognostic classification model in a large Italian population of sorafenib-treated patients. We also confirm a slightly better performance of the PROSASH-II compared with the HAP and SAP scores.

THU512

Use of a novel thyroid-stimulating hormone model for predicting the progression of hepatocellular carcinoma

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Background and Aims: Individuals with hepatocellular carcinoma (HCC) are at risk of tumor recurrence after surgical resection, which affects their survival. The present study aimed to establish a model for predicting tumor progression in patients with HCC.
Method: To develop and validate the efficacy of a novel prognostic model, a retrospective cohort with HCC (n = 1,005) at Beijing Ditan Hospital was enrolled from January 2008 and June 2017. Furthermore, a prospective cohort (n = 77) was recruited to validate the association between thyroid-stimulating hormone (TSH) levels and tumor progression in patients with HCC.
Results: The model used in predicting the progression of HCC included four variables (namely, Barcelona Clinic Liver Cancer [BCLC] stage, presence of portal vein tumor thrombus, alpha-fetoprotein level, and TSH level). The AUROC of the 1-year progression-free survival (PFS) model were 0.755 and 0.753 in the deriving cohort and validation cohort, respectively, and these values were significantly higher than those of the Child–Pugh score, Model for End-stage Liver Disease (MELD), tumor–lymph node–metastasis (TNM) staging system, Okuda classification, and CLIP score. A simple assessment using a nomogram showed the 1-year PFS rate of patients with HCC. In the prospective cohort, the KM curve showed that the high TSH level group had a shorter PFS than the low TSH level (p = 0.001).

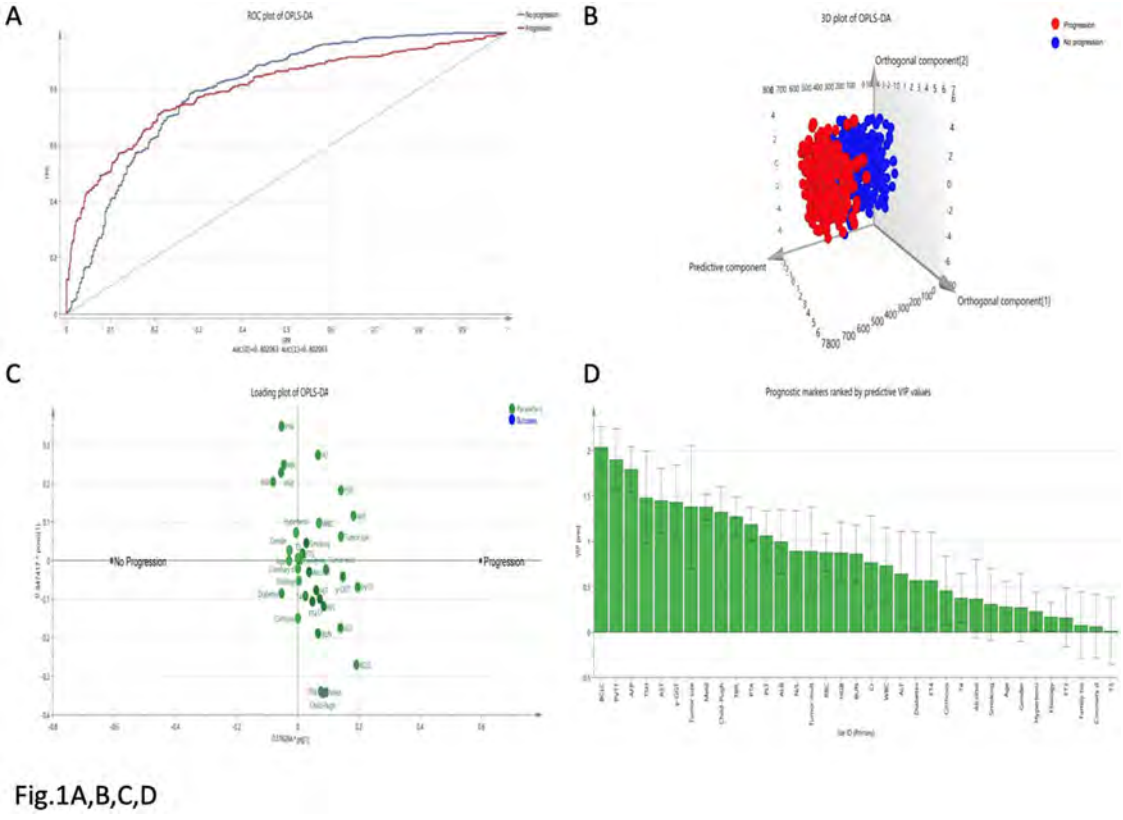

Fig. 1: (abstract: THU512) Orthogonal partial least squares discriminant analysis (OPLS-DA) of the prognosis of HCC. (A) Receiver operating characteristic (ROC) curve of OPLS-DA. (B) The OPLS-DA 3D plot of progression and no progression was distinguished using the predictive component: blue dots representing no progression and red dots indicating rogression. (C) Loading plot from the OPLS-DA of the progression and no progression groups. (D) When the predictive VIP (VIP-pred) value is higher, the ability to predict the progression of HCC is stronger.

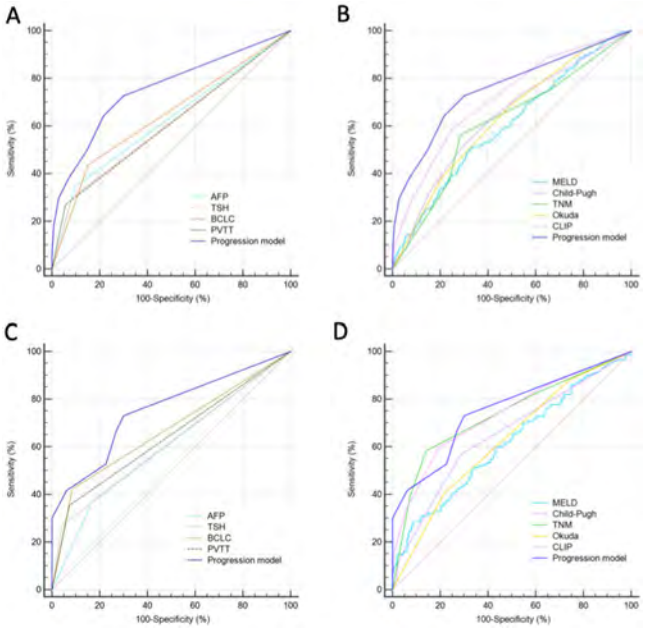

Fig. 2: (abstract: THU512): Receiver operating characteristic curves of the different models in predicting the 1-year PFS of patients with hepatocellular carcinoma. (A-B) Separate prognostic variables and other models in the deriving cohort. (C-D) Separate prognostic variables and other models in the validation cohort.

Conclusion: The prognostic model of HCC progression was superior to other well-known classical tumor scoring systems. A high TSH level was correlated to poor outcome, particularly those with advanced HCC.

THU513

A scoring system based on artificial neural network for predicting progression in HBV-related hepatocellular carcinoma

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Background and Aims: Disease progression is an important factor affecting the long-term survival in hepatocellular carcinoma (HCC). This study aimed to explore the prognostic factors that affect the progression of HCC and establish an individualized prediction model.
Method: We included 2,890 patients with hepatitis B-related HCC hospitalized at Beijing Ditan Hospital, Capital Medical University and randomly divided into training and validation cohort. Cox multivariate regression was used to analyze independent risk factors affecting the 1-year progression of HCC, and an artificial neural network model was constructed. C-index, calibration curve, and decision curve analysis were used to evaluate the performance of the model.
Results: Cox multivariate regression showed smoking history, a tumor number ≥ 2, tumor size ≥ 5 cm, portal vein tumor thrombus, WBC, NLR, γ-GGT, ALP, and AFP ≥ 400 ng/mL were risk factors for 1-year progression-free survival (PFS), while albumin and CD4T cell counts were protective factors in HCC patients. The AUROC of 1-year PFS in HCC patients was 0.866 (95% CI 0.848–0.884), which were higher than predicted by TNM, BCLC, Okuda, CLIP, CUPI, JIS, and ALBI scores ($P < 0.0001$). All patients were divided into high-, medium-, and low-risk groups, according to the ANNs model scores. Compared with the hazard ratios (HRs) of PFS in low-risk group, those in the high-risk group were 26.42 (95% CI 18.74–37.25; $P < 0.0001$) and 6.13 (95% CI 4.28–8.79; $P < 0.0001$) in the training and validation cohorts, respectively.

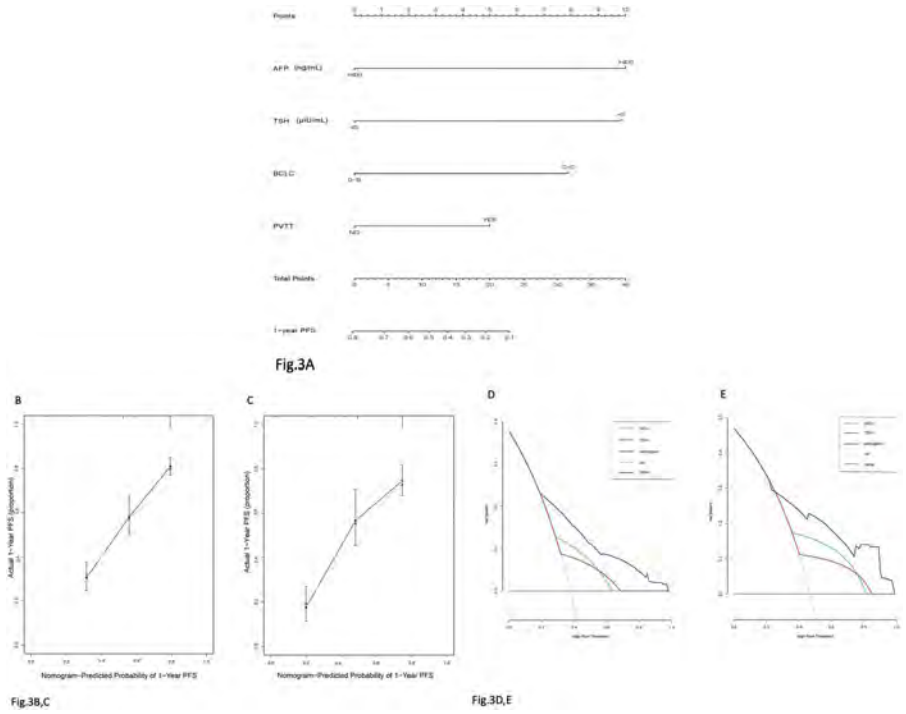

Fig. 3: (abstract: THU512): Prognostic nomogram and calibration curves and decision curve analysis. Nomogram predicted progression-free survival (PFS) (A) for HCC patients. The calibration curves for 1-year PFS (B, C) in the deriving and validation cohorts were identified. The nomogram-predicted probabilities of 1-year PFS (D, E) in the deriving and validation cohorts are compared with BCLC stage and TSH level.

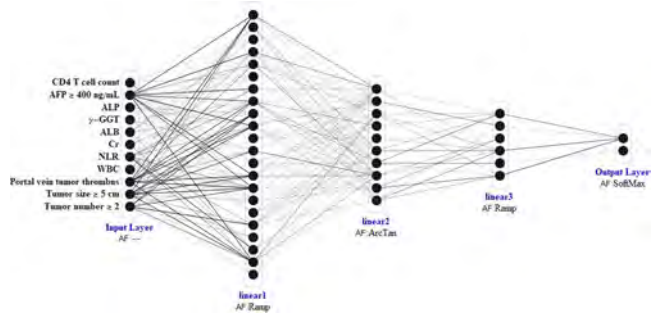

Fig. 2 ANN analysis of 1-year progression in patients with HBV-HCC.

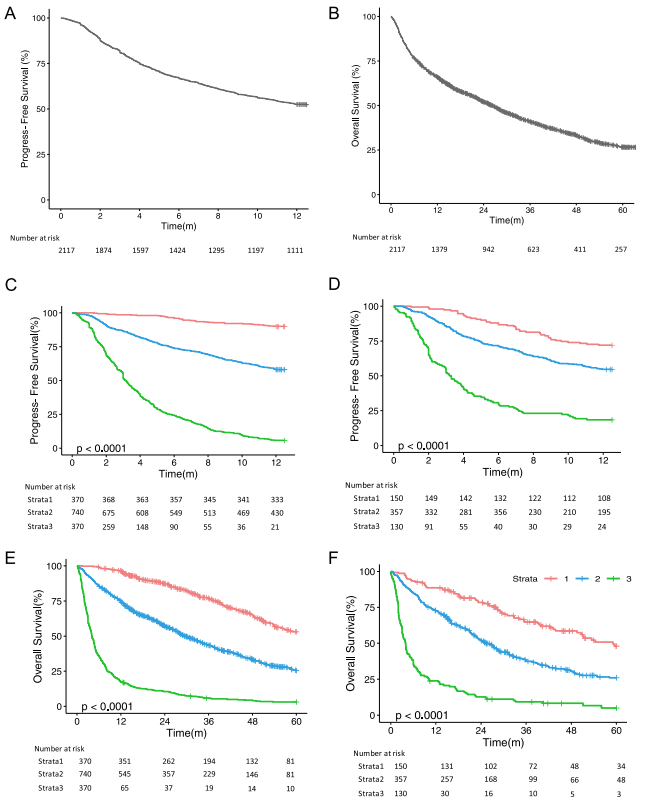

Fig. 4 The Kaplan-Meier survival curves of progress-free survival and overall survival in all HCC patients (A-B), training cohort (C-D), and validation cohort (E-F). C-F, comparison of survival distributions by ANNs model.

Conclusion: The ANNs model has good individualized prediction performance and is helpful to evaluate the disease progression of HCC in clinical practice.

THU514

Prediction of long-term survival of patients with hepatocellular carcinoma based on NK cells count novel model

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Background and Aims: Among all immune cells, NK cells, as the first line of defense against tumor, play a vital role. The purpose of our study is to observe whether the number of NK cells can predict the survival of patients with hepatocellular carcinoma (HCC).
Method: To develop a novel model, a retrospective cohort with HCC (n = 121) at Beijing Ditan Hospital was enrolled from January 2012 and June 2014. Furthermore, a prospective cohort (n = 58) was recruited to validate the association between NK cells count and survival in patients with HCC.
Results: The model used in predicting survival of HCC included four variables (namely, NK cells count, tumor size, tumor number, and AFP level). A simple assessment using a nomogram showed the 5-year OS rate of patients with HCC. The nomogram was divided into high, intermediate and low risk groups to predict the 5-years survival risk of HCC patients (p < 0.001), and there were significant differences in BCLC stage 0-B and BCLC stage C-D (p = 0.002, p = 0.0042). The decision tree showed that the 5-years death risk of HCC with low NK count (≤124.5) was 61.2%. In the prospective cohort, the contour line shows that low NK counts and high AFP level have more death of HCC. NK cells count in patients with advanced HCC was significantly lower than that in patients with early.
Conclusion: Our study emphasises the utility of NK cells count for exploring interactions between long-term survival and predictor variables.

THU515

Chronological improvement in long-term outcomes of surgical resection for patients with hepatocellular carcinoma: two large-volume center studies

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Background and Aims: As the treatment for underlying liver diseases developed, clinical outcomes of patients with hepatocellular carcinoma (HCC) has been improved. We investigated whether long-term outcomes following surgical resection in HCC patients were changed over time according to the etiology of liver disease.
Method: In this study, 1,579 consecutive patients who underwent surgical resection for HCC as an initial treatment between 2016 and 2013 at two large-volume centers in Korea (Seoul National University Hospital and Samsung Medical Center) were included. Study patients were divided into two groups by the year of operation: late-2000s (2006–2009: n = 612) or early-2010s group (2010–2013: n = 967). Primary and secondary endpoints were recurrence-free survival (RFS) and overall survival (OS), respectively.
Results: Median follow-up duration was 5.7 years in the late-2000s group and 5.0 years in the early-2010s group. Both RFS and OS were significantly longer in the early-2010s group among entire cohort (both log-rank p < 0.001) (panel A and B). Multivariable Cox analyses revealed that the early-2010s group was an independent predictor of both prolonged RFS (adjusted hazard ratio [aHR] = 0.81, 95% CI = 0.69–0.96, p = 0.01) and OS (aHR = 0.33, 95% CI = 0.24–0.45, p < 0.001) compared to the late-2000s group. When patients were categorized into the two subgroups according to underlying liver disease (hepatitis B virus [HBV], n = 1,230; and others, n = 349), the aHR of RFS was similar between two subgroups (HBV subgroup: aHR = 0.83, 95% CI = 0.69–0.99, p = 0.04; other subgroup: aHR = 0.83, 95% CI = 0.55–1.25, p = 0.36) (panel C and D). OS of early-2010s group was also significantly improved in both subgroups (HBV subgroup: aHR = 0.32, 95% CI = 0.22–0.45, p < 0.001; other subgroup: aHR = 0.29, 95% CI = 0.16–0.56, p < 0.001) (panel E and F). HRs were maintained after balancing baseline characteristics using inverse probability weighting.
Conclusion: Long-term clinical outcomes of surgical resection for the treatment of HCC were improved over time with approximately 30% decreased risk of recurrence or death.

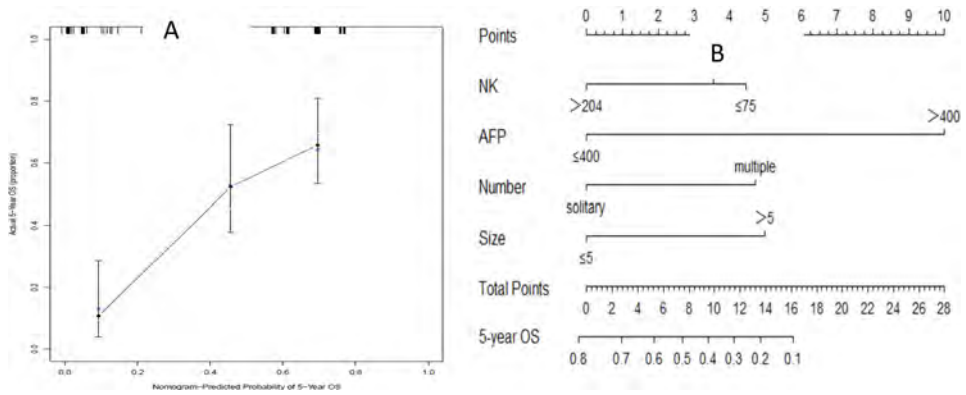

Figure 1: (abstract: THU514): Prognostic nomogram and calibration curves. Nomogram predicted overall survival (OS) (A) for HCC patients. To use the nomogram, the value of an individual patient is located on each variable axis, and a line is drawn upward to determine the number of points received for the value of each variable. The sum of these numbers is located on the total point axis, and a line is drawn downward to OS axes to determine the likelihood of 5-year OS. The calibration curves for 5-year OS (B) in the deriving cohorts were identified.

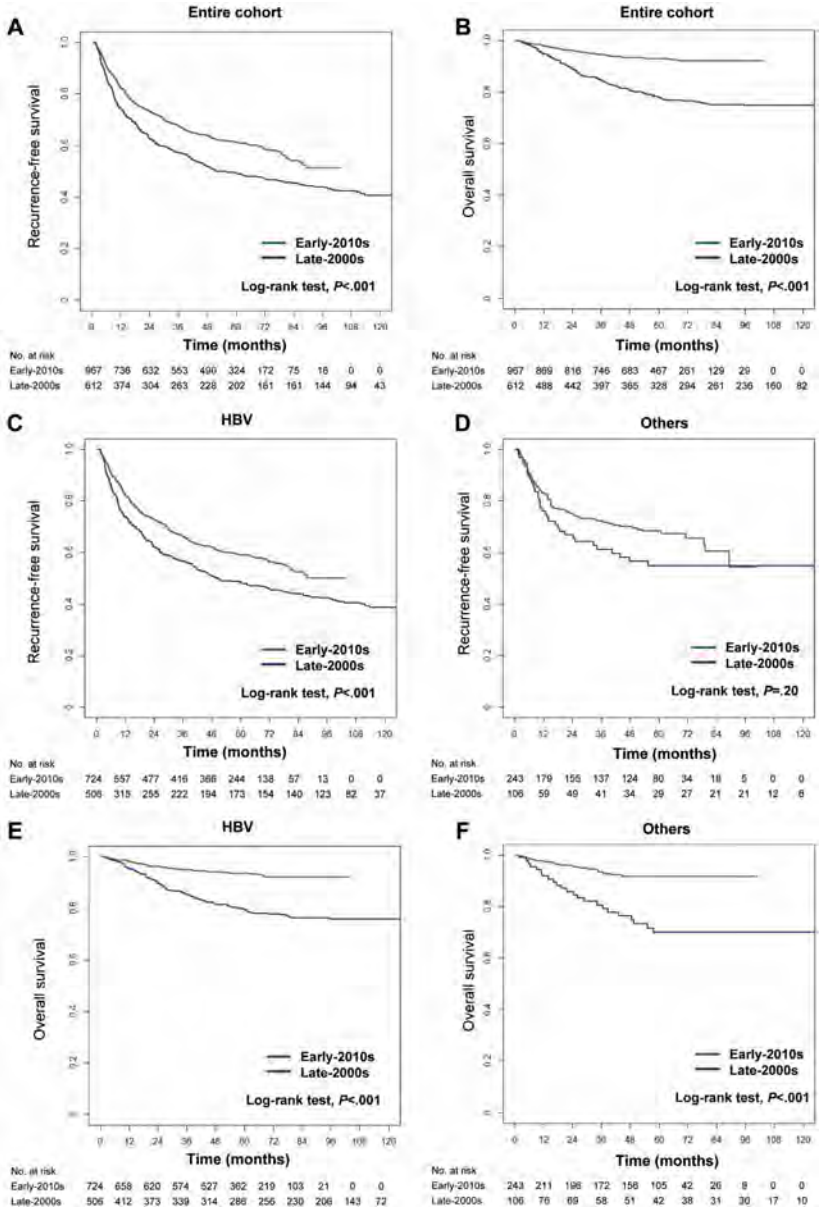

Figure: (abstract: THU515)

THU516

Glucose variability and risk of hepatocellular carcinoma in diabetic patients: a nationwide population-based study

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Background and Aims: Although it is well known that diabetes is a significant risk factor for hepatocellular carcinoma (HCC), exactly which metabolic parameters of diabetes are associated with HCC remains unexplored. The aim of this study was to investigate the relationship between glucose variability (GV) and HCC in diabetic patients through a nationwide population-based study.
Method: A population-based cohort study including 674,178 diabetic subjects participating in more than 3 health examinations within 5 years from the index year (2009–2010) were followed until the end of 2017. The coefficient of variation (CV), standard deviation, and variability independent of the mean were calculated as GV indices.
Results: During a median follow-up of 6.7 years, there were 5,494 cases of HCC. When we classified groups according to glucose level, the highest risk for HCC was observed when the basal blood glucose level was 180 mg/dL or greater [adjusted hazard ratio [aHR] 1.19, 95% confidence interval (CI), 1.08–1.31]. We observed increasing trends for the relationship between GV and HCC in multivariable Cox proportional analyses. The risk of HCC increased by 27% (aHR 1.27, 95% CI, 1.17–1.38) for the highest quartile of GV relative to the lowest quartile. These findings were consistent regardless of the presence of chronic viral hepatitis or cirrhosis, alcohol consumption, or body mass index. Subgroup analysis also yielded similar results.
Conclusion: GV is an independent predictor of HCC, even after adjusting for confounding factors. There was a linear relationship between increase in GV and prevalence of HCC. These results suggest that GV is helpful for identifying diabetic patients at high risk of HCC.

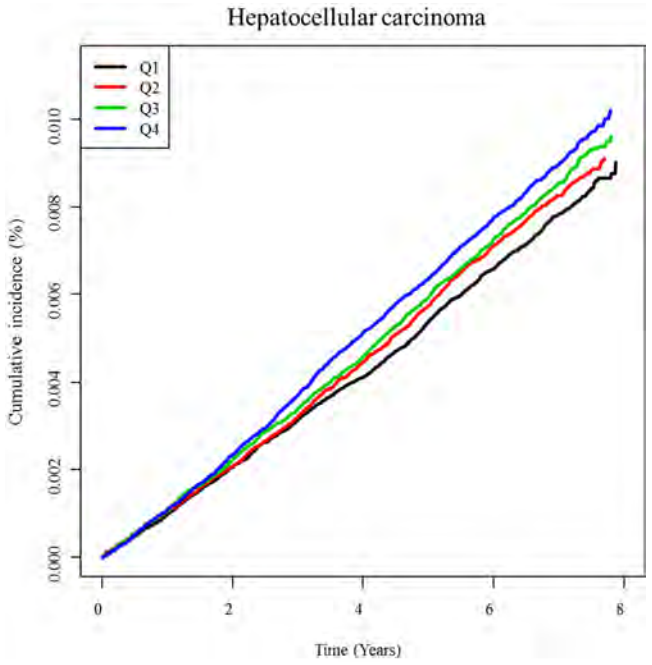

Figure: (abstract: THU516)

THU517

Estimation of hepatocellular carcinoma risk after hepatitis B surface antigen seroclearance

Yewan Park[1], Joo Hyun Oh[1], Myungji Goh[1], Dong Hyun Sinn[1], Jihye Kim[1], Geum-Yon Gwak[1], Seung Woon Paik[1], Wonseok Kang[1], Yong-Han Paik[1], Moon Seok Choi[1], Minseok Albert Kim[2], Jeonghoon Lee[2]. [1]*Samsung Medical Center, Internal Medicine, Seoul, Korea, Rep. of South;* [2]*Seoul National University Hospital, Internal Medicine, Seoul, Korea, Rep. of South*
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Background and Aims: The available evidence suggests that hepatocellular carcinoma (HCC) can develop after hepatitis B surface antigen (HBsAg) loss. However, whether HCC risk differs between antiviral therapy (AVT)-induced or spontaneous cases, and ways to identify at risk population remains unclear. We compared.
Method: A retrospective cohort of 1174 patients (median age: 56 years; 809 males; 151 with cirrhosis; 200 antiviral therapy (AVT)-induced cases) who achieved HBsAg seroclearance were analyzed for the development of HCC after HBsAg seroclearance.
Results: During a median 4.5 years of follow-up (range: 1.0–17.8 years), HCC was developed in 18 patients (1.5%). AVT-induced patients showed higher incidence of HCC than spontaneous cases (5-years HCC incidence rate of 0.7% vs. 3.9%, $p < 0.001$). No HCC cases were identified among patients who achieved HBsAg seroclearance at <50 years of age, either spontaneously (n = 780) or by AVT (n = 116). For those who achieved HBsAg seroclearance after 50 years of age, the 5-year cumulative incidence rate of HCC was higher for AVT-induced cases (0.9% vs. 6.8%, $p < 0.001$), with higher hazard ratio (4.99, 95% confidence interval, 1.78–14.01) for HCC in multivariable adjusted analysis.
Conclusion: Patients who achieved HBsAg seroclearance by AVT showed higher risk for HCC, especially for those who achieved HBsAg seroclearance after 50 years. This imply that clinical benefit of HBsAg secoclearance by AVT can be more beneficial when induced at early age.

THU518

Indeterminate nodules in hepatocellular carcinoma surveillance: an analysis of the frequency, outcomes and costs

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Background and Aims: Current guidelines recommend biannual hepatocellular carcinoma (HCC) surveillance with ultrasound scan (USS) for patients with cirrhosis. However, USS is not diagnostic for HCC, therefore USS-detected nodules are deemed indeterminate (INs), which require further investigation to confirm whether these are benign (INb) or HCCs. We investigated the frequency and outcomes of INs in a single-centre HCC surveillance programme and the downstream costs associated with IN detection.
Method: Retrospective data were collected from electronic records of adult cirrhotic patients attending St Mary's Hospital, London between 01/01/2014 and 01/01/2019. Relevant data were extracted for all liver imaging, patient demographics, baseline laboratory results and clinical evidence of liver decompensation. Cost of scans were calculated based on NHS tariffs and Public Health England guidance. SPSS was used for analysis.
Results: We identified n = 302 patients in total (Fig. 1). The mean follow-up was 3.3 years, median age was 60 years, 69% were male and 57% Caucasian. Less than 30% of patients adhered to 6-monthly surveillance for the whole follow-up period. 19% (n = 58) of patients were found to have INs. Upon further investigation, 9% (n = 28) were diagnosed with HCCs and 9% (n = 28) were diagnosed with INbs. 1% (n = 2) were still undergoing investigation at the end of the study period.

Table 1: (abstract: THU517): Factors associated with hepatocellular carcinoma development among overall patients (n = 1174) and patients aged over 50 years (n = 896)

	Overall (n = 1174)				Age ≥ 50 years (n = 896)			
	Univariable HR (95% CI)	*p*-value	Multivariable HR (95% CI)	*p*-value	Univariable HR (95% CI)	p-value	Multivariable HR (95% CI)	*p*-value
Age (per year)	1.04 (0.99–1.10)	0.104			0.99 (0.92–1.06)	0.762		
Male (vs. female)	7.15 (0.95–53.7)	0.056			7.02 (0.93–52.80)	0.058		
Cirrhosis (vs. no)	7.08 (2.80–17.8)	<0.001			6.92 (2.75–17.45)	<0.001		
Platelet count ($m^3/\mu l$)	0.99 (0.99–1.00)	0.202			1.00 (0.99–1.00)	0.268		
Elevated ALT* (vs. no)	1.55 (0.51–4.74)	0.438	4.62 (1.70–12.52)	0.003	1.91 (0.63–5.82)	0.255	3.79 (1.35–0.63)	0.011
AVT (vs. no)	6.03 (2.36–15.4)	0.001	3.57 (1.31–9.72)	0.013	8.48 (3.34–21.51)	<0.001	4.99 (1.78–4.01)	0.001

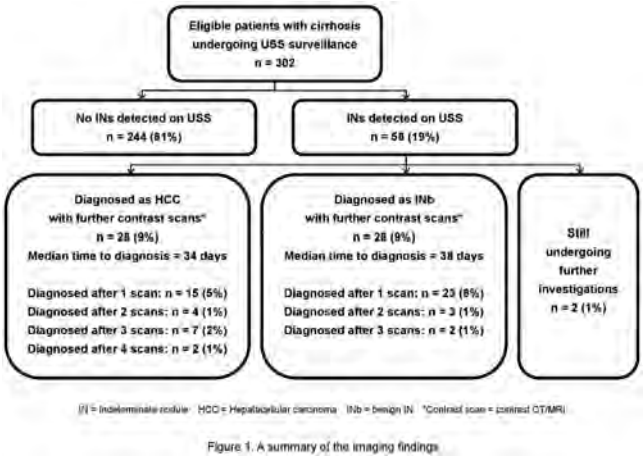

Figure 1. A summary of the imaging findings

On average, an additional 1.3 contrast scans were performed per patient with INb, which adds £175 to the cost per patient over a five-year period. Overall, this amounts to 4.4% of the total HCC surveillance cost in this study. Extrapolated nationally, NHS spending is estimated to be £972,000 for additional scans diagnosing INbs over a five-year period.

The median time to diagnose or exclude HCC was over 1 month. 71% of HCCs were detected at a potentially curable stage. Patients with HCC were significantly more likely to have varices (p = 0.02) and lower serum albumin (p = 0.01) than those with INbs. Older age was independently associated with HCC risk.

Conclusion: Although most HCCs diagnosed on surveillance are at a potentially curative stage, adherence to surveillance is poor. The percentage of INs that are eventually diagnosed as HCC or INb are similar. More severe liver disease and older age are associated with HCC. Substantial delays can occur before INs are definitively diagnosed; the burden on patients and resource implications of reducing diagnostic delays require further study.

THU519

Serum creatinine/cystatin C ratio has a potential as a useful surrogate marker for evaluation of muscle mass volume in patients with hepatocellular carcinoma

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Background and Aims: Sarcopenia is considered a poor prognostic factor for many diseases and malignancies, including hepatocellular carcinoma (HCC). Muscle mass volume (MMV), which is required for sarcopenia diagnosis, is generally measured by computed tomography (CT) and bioelectrical impedance analysis. Due to their complicated methodologies and medical costs for examinations, more convenient and universal approaches for MMV are required. Recently, the ratio between serum creatinine (Cre) and cystatin C (CysC) (Cre/CysC) was reported to potentially be a new surrogate marker for MMV in several diseases. The present study aimed to clarify the relationship between Cre/CysC and MMV in HCC patients and explore the possibility of easy MMV evaluation.

Method: We identified consecutive newly diagnosed and initially treated HCC patients from our institutional database between June 2009 and December 2016. We excluded patients who lacked even one of the following parameters: abdominal CT image for assessing MMV, serum Cre level, and CysC level. MMV was expressed by the skeletal muscle index at L3 (L3-SMI) on CT. The correlation of Cre/CysC with L3-SMI was analyzed. A prediction model for L3-SMI was created using multiple regression analysis. Furthermore, we collected the measurement data of Cre/CysC and L3-SMI obtained more than 6 months after the initial measurement and validated the model.

Results: The study included 614 patients (age, 70.1 ± 9.5 years; 428 males). We found a significant correlation between Cre/CysC and L3-SMI (r = 0.307, p < 0.001). In patients with serum Cre levels higher than the upper normal limit, the correlation was not significant (r = 0.121, p = 0.252). However, in those with normal serum Cre levels, the correlation was strong (r = 0.356, p < 0.001). We attempted to develop a new prediction model in the normal serum Cre population (n = 522) (Figure). The model showed significant R-square in the original cohort (0.637) and internal validity by using bootstrap verification (0.633, 95%CI: 0.628–0.638). Of the 522 patients, 376 had datasets of abdominal CT, serum Cre, and CysC at different time points. Our prediction model was validated in the normal serum Cre population (n = 297, R-square: 0.46).

L3-SMI =

12.6*Cre/CysC + 1.40*BMI + 0.54*Alb – 0.14*Age + 10.4 (male)

12.6*Cre/CysC + 1.40*BMI + 0.54*Alb – 0.14*Age + 3.96 (female)

Conclusion: Our model, which was based on Cre/CysC, had the potential to estimate L3-SMI. Monitoring sarcopenia in HCC patients closely by using these two simple parameters will change daily practice. Our model should be validated in other patient cohorts of not only HCC but also other diseases.

EASL JOURNAL OF HEPATOLOGY

NAFLD: Diagnostics and non-invasive assessment

FRI001

The development of the NAF3 score to accurately predict the presence of active NASH with advanced fibrosis

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Background and Aims: Several pharmacologic agents that target patients with advanced NASH are in development. Phase 3 clinical trials included patients with evidence of active disease defined as NAFLD activity score (NAS) of 4 or higher AND fibrosis stage 2–3 (F2-F3). Given potential for side effects and relatively low efficacy, clinicians are likely to restrict the use of new agents to patients with NAS = />4 with F3; therefore, noninvasive identification of those patients is urgently needed to optimize the use of new agents. The aim of this study was to develop a new noninvasive score using readily available clinical data and liver stiffness measure by transient elastography (TE) to predict NAS ≥ 4 + F3 in patients with biopsy-proven disease.
Method: Patients from 5 U.S. major centers who underwent liver biopsy, laboratory assessment, and TE measurements within 6 months were included. Liver histology was assessed by experienced pathologists blinded to clinical data. The grade of steatosis, hepatocyte ballooning, and inflammatory activity was measured by Kleiner's criteria and the stage of fibrosis was recorded (F0-F4). Multivariable backward stepwise logistic regression was used to build a model to identify patients with NAS ≥ 4 + F3 and C-statistics with AUROC were used to assess the accuracy of the model.
Results: Our cohort consisted of 282 patients with biopsy-proven disease with a mean age of 56.4 ± 11.8 years and mean BMI of 33.7 ± 7.7 kg/m^2. The mean platelet count was 228.8 ± 78.9 k/uL, mean AST of 45.5 U/L and ALT of 58.3 U/L. The M probe was used in 152 patients and the XL probe in 97 patients to measure liver stiffness with a mean of 12.5 ± 9.9 kPa. NASH was present in 67% (n = 159) and 24.8% (n = 70) of patients had NAS ≥ 4 + F3. We developed a model called NAF3 score to predict the presence of NAS ≥ 4 + F3 on liver biopsy using the following variables: Age, sex, AST, liver stiffness, bilirubin, HDL cholesterol, and the presence of diabetes. The AUROC for the new score was 0.836 (95% CI 0.754–0.918). Internal cross validation of the model revealed mean AUROC of 0.7772 (95% CI: 0.6792, 0.8240).
Conclusion: In a large multi-center cohort of patients with the full spectrum of NAFLD, the NAF3 score using liver stiffness and clinical variables can accurately identify patients with NAS ≥ 4 + F3. This score is a promising tool for selecting patients for pharmacologic agents. Further validation is needed.

FRI002

Advanced transcriptomics identifies the tweak receptor as a novel biomarker in non-alcoholic steatohepatitis: biomarker discovery from gene expression signature to plasma protein

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Background and Aims: Obesity and diabetes are major risk factors for non-alcoholic steatohepatitis (NASH). There is no specific clinical phenotype that permits diagnosis of NASH. Hence, there is an immediate need for validated and robust clinical biomarker assays to identify disease stages and direct treatment intervention strategies.
Method: Genes regulated in diet-induced obese (DIO)-NASH mice were identified using hepatic RNA sequencing datasets from DIO-NASH mice (AMLN diet; 40% fat, 20% fructose, 2% cholesterol) as compared to standard high-fat diet (60% high fat diet) and lean chow fed mice. Several novel NASH specific biomarker candidates were identified, including tumor necrosis factor receptor superfamily member 12A (tnfrsf12a), encoding the TWEAK receptor (TWEAKR), a candidate biomarker not previously related to NASH progression. TWEAKR levels were determined by ELISA (R&D Systems) in plasma from C57Bl/6J and ob/ob mice fed AMLN diet for 58 and 20 weeks, respectively.
Results: Single-cell sequencing of liver cells revealed expression of the lead biomarker candidate gene encoding TWEAKR, tnfrsf12a, to be confined to epithelial cells in chow mice, and upregulated in both these cells and in specific immune cell subsets in DIO-NASH mice. To verify translatability, expression of tnfrsf12a was compared to gene expression profiles in liver biopsies from healthy human individuals and NAFLD/NASH patients, showing excellent correspondence. Plasma TWEAKR levels were significantly increased in DIO-NASH mice compared to chow-fed control mice (189 ± 14 vs. 91 ± 4 ng/mL, $p < 0.001$). Returning mice to chow diet for 8 weeks normalized plasma levels (105 ± 6 ng/mL). The same pattern was observed in the more severe ob/ob DIO-NASH mouse model (ob/ob DIO-NASH 353 ± 25; ob/ob DIO-NASH reversal 178 ± 9, ob/ob chow 158 ± 10 ng/mL, $p < 0.001$). Plasma TWEAKR levels correlated to histological findings of inflammation and liver fibrosis.
Conclusion: We identified a panel of novel NASH-specific biomarker candidate genes by combining multiple hepatic RNA sequencing datasets in mouse and man. A lead biomarker candidate gene, tnfrsf12a, was subsequently identified to be elevated also at the protein level in plasma from two validated DIO-NASH mouse models. The data demonstrate methodological proof of concept and is considered of high value for the development of clinical biomarkers enabling patient stratification for future NASH treatment options and clinical trials.

FRI003

Machine learning models identify novel histologic features predictive of clinical disease progression in patients with advanced fibrosis due to non-alcoholic steatohepatitis

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Background and Aims: Fibrosis is the primary determinant of disease progression in patients with nonalcoholic steatohepatitis (NASH), but the prognostic impact of other histological features is unclear. We used a machine learning (ML) approach and biopsy images to identify novel morphologic features and associations with disease progression in patients with advanced fibrosis due to NASH.
Method: Biopsies from 644 patients screened for a phase 3 trial of selonsertib (STELLAR-4) were scored by a central pathologist (CP) according to the NASH CRN and Ishak staging systems. The PathAI research platform (PathAI, Boston, MA) was applied to train a convolutional neural network (CNN) with >68,000 annotations (e.g. steatosis, ballooning, lobular/portal inflammation) collected from 75 board-certified pathologists on images of H&E and trichrome (TC)-stained slides. For staging fibrosis, CNN models were trained using slide-level pathologist scores to recognize unique patterns associated with each stage within fibrotic regions of TC images. These region-based scores were summarized for each slide. In total, 202 features were extracted from biopsy images from NASH patients (F3-F4) enrolled in the STELLAR trials. Cox regression was used to identify associations between these features with progression to cirrhosis in F3 patients, and liver-related events (e.g. decompensation, transplantation, death) in those with cirrhosis (F4).
Results: 1526 NASH patients with F3-F4 fibrosis (median age 59 yrs, 73% diabetic, 52% F4) were included. During a median follow-up of 16.5 mos, 14.5% (105/726) of F3 patients progressed to cirrhosis, and over 15.9 mos, 2.8% (22/800) of F4 patients had liver-related events. Progression to cirrhosis was associated with greater proportions of all Ishak scored area consistent with Ishak 6 fibrosis and greater proportions of total tissue area consistent with portal inflammation (Figure). Similar associations with clinical events was observed in F4 patients, with hepatocellular ballooning also associated with clinical events. In F3, a greater proportion of Ishak scored area consistent with Ishak 1 fibrosis and of total tissue area consistent with steatosis were associated with a reduced risk of progression. In F4 patients, a greater proportion of total tissue area consistent was steatosis was similarly protective, while proportion of Ishak Stage 1 Fibrosis over Ishak scored area trended towards protective.

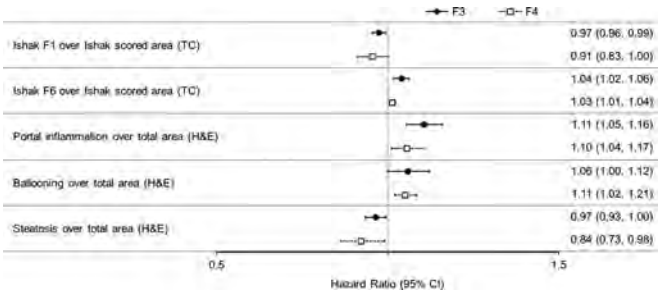

Figure: Associations Between ML-Based Morphological Features with Disease Progression in Patients with Advanced Fibrosis Due to NASH.

Conclusion: Liver histological evaluation using this automated, ML approach identified novel features associated with progression in NASH patients with advanced fibrosis. These data support the utility of ML approaches to evaluation of liver histology as endpoints in NASH clinical trials.

FRI004

Serum proteomics identifies biomarkers of fibrotic severity in NASH patients

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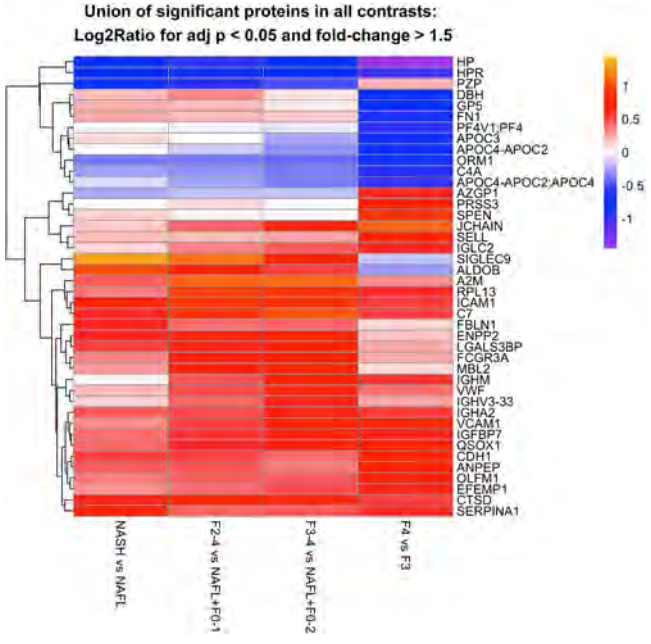
Background and Aims: Non-alcoholic steatohepatitis (NASH) affects 3–12% of the US population and can progress to cirrhosis, liver failure and hepatocellular cancer. There is a strong need for noninvasive alternatives to liver biopsy. In this study we sought to identify serum biomarkers that associate with more advanced fibrosis severity in NASH.
Method: Sera from 420 biopsy-proven NASH (F0-F4) and NAFL (fatty liver) patients were randomized into 6 × 96-well plates. We analyzed samples by nano-liquid chromatography mass spectrometry (LCMS) using data-independent acquisition (DIA), and processed raw data in Spectronaut (Biognosys AG). Of 522 total detected proteins, 272 proteins were present in >75% of samples for analysis. We used limma to model how log2, quantile-normalized protein data associate with NASH (F0-F4 vs NAFL), significant fibrosis (F2-F4 vs NAFL and F0-F1), advanced fibrosis (F3-F4 vs NAFL and F0-F2), and NASH F4 vs F3. In parallel, 58 potential fibrotic biomarkers were assayed from the same patient sera using the Luminex platform, a multiplexed ELISA assay. Data were Arcsinh-transformed and locally-estimated-scatterplot-smoothing (LOESS)-normalized prior to limma modeling. All data were corrected for multiple testing using Benjamini-Hochberg.



Results: We identified many proteins associated with NASH compared to NAFL, and with fibrotic severity (Figure). We found 31 proteins associated with NASH, 84 with significant fibrosis, 100 with advanced fibrosis, and 79 with NASH F4 vs F3 (adjusted p = 0.05).

These include novel and reported biomarkers of fibrosis, cirrhosis, and NASH. In addition, 9 proteins were assayed in both the LCMS and Luminex data. For the advanced fibrosis contrast 4 proteins were significant by both LCMS and Luminex, 1 was significant by only Luminex with concordance of direction, and 4 were never significant.
Conclusion: Using a large bank of NASH and NAFL sera, we identified proteins that associate with fibrotic severity of NASH, which comprise both novel and previously known biomarkers. Some of these we confirmed by other assays, including several immunoglobulins. Importantly, signatures distinguishing NASH F4 from NASH F3 may help diagnose asymptomatic F4 patients who are at high risk to develop end stage liver disease. These biomarkers may aid in the development of novel non-invasive models to classify disease stages and enable patient stratification. Further investigation is warranted to confirm the findings using independent quantitative assays.

FRI005

Performance of non-invasive fibrosis tests among non-alcoholic fatty liver disease (NAFLD) patients with normal alanine aminotransferase (ALT): data from a large North American primary care NAFLD pathway

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Background and Aims: Recent studies risk stratifying NAFLD patients within primary care have focused on patients with elevated transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]). Therefore, we used data from the Calgary NAFLD clinical care pathway (CNCCP) to compare performance of non-invasive liver fibrosis tests FIB-4, NAFLD fibrosis score (NFS), and 2-dimensional shearwave elastography (SWE) in NAFLD patients based on having elevated baseline ALT levels.
Method: The CNCCP was developed as a partnership to enable primary care physicians (PCP) to risk-stratify NAFLD patients within primary care. PCPs can directly access the CNCCP for their patients with any of the following conditions: overweight, obesity, diabetes mellitus, elevated liver enzymes, or fatty liver detected by prior imaging. Patients with suspected NAFLD (i.e. other causes of chronic liver disease excluded) were then assessed by SWE, ordered directly by PCPs. NAFLD patients with liver stiffness by SWE ≥ 8 kPa (or inconclusive result) were referred to hepatology, and those with SWE <8.0 kPa were managed by their PCPs using a standardized CNCCP management pathway. ALT of 30 U/L for men and 25 U/L for women were considered the upper limit of normal.
Results: 1,944 NAFLD patients were enrolled in the CNCCP between March-October 2018. Within this patient cohort there were 577 (29.7%) patients with a normal ALT at enrollment in the CNCCP (baseline). NAFLD patients with normal ALT were likely older (median age: 57 vs. 54, $p < 0.001$) than patients with elevated ALT. Patients with normal and abnormal baseline ALT levels were similar according to sex, body mass index (BMI), having diabetes mellitus or hypertension. Patients with elevated ALT levels had similar FIB-4 scores as those patients with normal ALT levels (median 1.01 vs. 0.97, $p = 0.117$), but had lower NFS scores (median: −1.24 vs. −0.71, $p < 0.001$) and higher SWE results (4.5 vs. 4.3 kPa, $p < 0.001$). 26.6% of patients in the normal ALT cohort had FIB-4 >1.30, compared to 33.6% in the elevated ALT cohort ($p = 0.016$). 69.2% of patients with normal ALT levels had NFS >−1.45, compared to 54.7% with elevated ALT ($p = 0.001$). In addition, 3.3% of patients with normal ALT had elevated liver stiffness (SWE ≥ 8 kPa), compared to 3.5% with elevated ALT ($p = 0.809$). In adjusted logistic regression analyses, elevated ALT was an independent predictor of FIB>1.30 (adjusted OR 2.09, 95%CI: 1.51–2.91) and NFS >−1.45 (aOR: 0.51: 0.35–0.76), but was not a predictor of SWE>8.0 kPa (aOR: 1.44, 0.87–2.39).
Conclusion: In a large primary care-driven NAFLD pathway, 1/3 of patients had normal ALT levels (within recommended sex-based cutoffs). Elevated ALT associated inconsistently with serum-based fibrosis markers and liver stiffness. Therefore, risk-stratification of NAFLD patients within primary care should not be limited to patients with elevated transaminases.

FRI006

Non-invasive detection of NASH and significant fibrosis in NAFLD patients with low FIB-4

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Background and Aims: Non-alcoholic steatohepatitis (NASH) and fibrosis play critical roles for the prognosis of patients with non-alcoholic fatty liver disease (NAFLD). Non-invasive methods to identify patients at risk for NASH or fibrosis are therefore crucial for disease management. The FIB-4 score, which is based on widely available and simple parameters (age, transaminases and platelets), has a high negative predictive value for advanced fibrosis (>90%) and has been therefore suggested as initial diagnostic approach. However, there is increasing evidence that also patients with NASH and early fibrosis are at significant risk of disease progression and complications, emphasizing the need for improved non-invasive risk stratification in NAFLD. Because hepatocyte apoptosis plays an early role in NASH pathogenesis, we evaluated whether the apoptosis biomarker M30, a neo-antigen generated by caspase-mediated keratin-18 cleavage, might identify NAFLD patients who are at risk of NASH and fibrosis despite low FIB-4 values.
Method and Results: Serum M30 levels were assessed by ELISA in combination with FIB-4 in a cohort of 103 patients with histological confirmed NAFLD. The majority of patients with low FIB-4 (cut-off value <1.3) revealed increased M30 levels (>200 U/L) and more than 80% of those had NASH, mostly with histological signs of fibrosis (43% of them with F2/F3 fibrosis). Importantly, most patients with FIB-4 <1.3 who revealed histological NASH despite non-elevated M30 levels showed no fibrosis. NASH was also detected in all patients with an intermediate FIB-4 score, i.e. between the low and high cut-off value (1.3 to 2.67), and elevated M30 levels, from which 81% showed fibrosis (F2-F4 fibrosis in almost half of cases). Similar results were obtained when considering a FIB-4 cut-off range of 1.3 to 3.25.
Conclusion: The combination of the M30 biomarker with FIB-4 enables a more reliable identification of patients with increased risk of progressed NAFLD and might be helpful for deciding which patient should be referred to a hepatologist and considered for liver biopsy.

FRI008

Predictive modelling to identify and characterize fast progressors among patients with non-alcoholic steatohepatitis (NASH)

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Background and Aims: A subset of patients with non–alcoholic fatty liver disease (NALFD) and non-alcoholic steatohepatitis (NASH) progress more rapidly to cirrhosis or hepatocellular carcinoma (HCC) than typical patients. The purpose of this study was to develop a machine learning model to predict the progression risk to

end-stage liver disease using data available from standard clinical care and electronic health care records.

Method: The study was conducted in the Optum Electronic Health records (2007–2018 data from the United States). The study cohort was defined as patients with a diagnosis of cirrhosis or HCC (based on International Classification of Diseases codes ICD-9/ICD-10) most likely due to NAFLD/NASH after excluding any other causes of liver disease. Time of progression was established retrospectively from the date of cirrhosis or HCC to the first evidence of disease (index date), which was the first diagnosis of either NASH, NAFLD, or one of several comorbidities (e.g. type 2 diabetes, obesity) used as proxies. Patients were grouped by time to progression from the first evidence of disease to cirrhosis or HCC: fast progressors (<3 years), intermediate progressors (3 to 6 years), standard progressors (6–10 years). Each class of the cohort was profiled and statistical testing to identify differences between these classes was performed. A model to predict fast progressors class was developed and main covariates that separate fast and standard progressors were determined. Multiple machine learning classification techniques were tested and the best performing model selected. Covariates included: laboratory tests and observations; comorbidities; treatments for comorbidities; and rate of change of laboratory tests and observations.

Results: The study included 4,419 patients with cirrhosis (96.1%) or HCC (3.9%) due to NAFLD/NASH. Mean (standard deviation) age was 63.0 (12.6), BMI 34.9 (7.3), 65% were female, and the most common comorbidities were hypertension (59%), hyperlipidemia (54%), and type 2 diabetes (43%). Among these patients, 1,087 fast progressors, 2,070 intermediate progressors, and 992 standard progressors were identified. These three classes exhibited significantly different clinical and laboratory features with 55 out of 112 tested covariates separating fast progressors from standard progressors. These include age at cirrhosis/HCC, platelet count, albumin, aspartate aminotransferase, and triglycerides.

Conclusion: These results suggest that patients with different progression rates to end-stage liver disease could be identified in real-world medical records and support the finalization of a predictive algorithm for identification of NAFLD/NASH patients with the highest risk of progression.

FRI009

Non-invasive tests for assessing fibrosis in patients with non-alcoholic fatty liver disease: an evaluation of combining test results

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Background and Aims: Fibrosis in non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) is often assessed histologically. However, liver biopsy is expensive, invasive, and can be associated with sampling variations. Multiple non-invasive tests (NITs) have been developed to assess hepatic fibrosis but have suboptimal performance characteristics when used individually. The aim of this analysis is to provide a construct to assess the potential utility of combining NITs based on literature and identify key issues when developing a multi-test testing strategy.

Method: Primary literature in English on 7 NITs, including NAFLD Fibrosis Score (NFS), Fibrosis-4 (FIB-4) index, aspartate aminotransferase-to-platelet ratio index (APRI), enhanced liver fibrosis (ELF) panel, FibroSURE, transient elastography (TE), and magnetic resonance elastography (MRE), for fibrosis assessment in NAFLD and NASH patients was reviewed. Study characteristics, NIT attributes and test performance measures (e.g., sensitivity, specificity) were abstracted. Sensitivity and specificity were combined in probabilistic calculations to approximate parallel (i.e., simultaneous) or serial (i.e., sequential) test strategies. Pairwise test combinations were limited to those within specific studies to reduce spectrum bias.

Results: Data from 61 full text publications were abstracted, yielding 750 records on test performance for various subpopulations and NITs. Combinations in which both tests must be positive reduced sensitivity, but increased specificity; the opposite was true with testing in which only one of the tests was required to be positive. Results varied depending on the study from which combinations were calculated, individual study populations, and level of fibrosis detected. Amongst all pairwise combinations explored in this limited pilot - APRI or NFS, and Fibroscan or NFS - had both sensitivity and specificity greater than 80% for detecting fibrosis greater than or equal to stage 2.

Conclusion: This exploratory examination based on probabilistic calculations of the literature on NITs and fibrosis in NASH/NAFLD found the test performance of combinations to be variable. Pairwise combinations of NITs in which either test can be positive via a parallel or serial process could increase sensitivity for accurately staging fibrosis, reducing the need for liver biopsy. Additional research is needed to account for spectrum bias and multiple threshold cutpoints.

FRI010

^{13}C-Octanoate breath test in a predictive score for the diagnosis of non-alcoholic steatohepatitis

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Background and Aims: Many studies have highlighted the importance of identifying the Nonalcoholic Steatohepatitis (NASH) subgroup, which carries a higher risk of morbidity/mortality with important prognostic implications. Hepatic mitochondrial dysfunction has been involved in progression of Nonalcoholic Fatty Liver to NASH especially by oxidative stress. The ^{13}C-Octanoate breath test (OBT), enables mitochondrial activity evaluation, as a source of oxidative stress, implicated in the development of nonalcoholic steatohepatitis. The aim is to develop a non-invasive score for identifying NASH among patients diagnosed with NAFLD.

Method: 68 patients with histological proven NAFLD were included in the study. Liver biopsy was performed for abnormal liver function tests and suspected NAFLD by greyscale ultrasonography. All patients underwent standard biochemistry as well as stable isotope breath tests with ^{13}C-Octanoate (OBT). The relevant parameters were determined using Independent Samples T test and incorporated into a formula using logistic regression. The formula was calculated as (74 X [C13-Octanoate Dose/h at 30 min] + 15 X [Cholesterol] + 7 X [Triglycerides] – 35)/100. The accuracy of the score was evaluated using the area under the ROC curve and its ability to establish diagnosis using a predetermined cutoff (35) was evaluated using chi-square test

Results: Patients were divided in two groups according to the histologic characteristics: 32 patients with steatosis and 36 patients with NASH. Patients with steatohepatitis had significantly increased 13C-Octanoate results (23.54 vs 18.29, $p < 0.001$), increased cholesterol (202.92 vs 172.45 $p = 0.030$) and increased triglycerides (178.95 vs.124.84 $p = 0.005$). The score had an area under the ROC curve of 0.953 (95%CI 0.863–1.000, $p < 0.001$). Using a cutoff value of 35, the score had significant results in the chi-squared test ($p < 0.001$) and presented with a sensitivity of 100% (95%CI 92.13%–100%), specificity of 95.65% (95%CI 78,05%–99.89%), PPV of 97.83% (95%CI 86.87%–99.67%) and NPV of 100%. Overall accuracy was 98.53% (95%CI 92.08–99.96%).

Conclusion: A non-invasive score containing the main parameters associated with NASH pathogenesis, may be useful for diagnosis, avoiding the need for many liver biopsies.

FRI011

Interplay between metabolic derangement, biomarkers of collagen remodeling and macrophage activation in non-diabetic patients with non-alcoholic fatty liver disease

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Background and Aims: The pathogenesis of Non-Alcoholic Fatty Liver Disease (NAFLD) and steatohepatitis (NASH) is likely due to the interaction between a deranged metabolic milieu and local mediators of hepatic inflammation and fibrosis. We investigated a panel of serum non-invasive biomarkers of collagen remodelling and explored their association with metabolic derangements and liver damage to elucidate their complex interplay in a well-characterized cohort of non-diabetic NAFLD patients.
Method: We enrolled 52 non-diabetic subjects with biopsy proven NAFLD who underwent a double tracers oral glucose tolerance test. Using tracers data we measured endogenous glucose production (EGP) and lipolysis by glycerol rate of appearance (GlycRa) and we calculated indexes of IR in the liver (Hep-IR = EGP × insulin) and in the adipose tissue (Lipo-IR = GlycRa × insulin and AT-IR = free fatty acids × insulin). Fasting c-peptide (CP) levels were measured using a chemiluminescence assay. Fibrogenesis biomarkers PRO-C3 and PRO-C6 as well as macrophage activation biomarker sCD163, were measured by ELISA. Histology was scored according to Kleiner.
Results: Overall, fasting CP, PRO-C3, PRO-C6 levels directly correlated with BMI and waist circumference (all $p < 0.03$). Among IR indexes, PRO-C3 and PRO-C6 correlated with Hep-IR ($r_S = 0.32$, $p = 0.025$; $r_S = 0.38$, $p = 0.006$), adipo-IR (both Lipo-IR [$r_S = 0.36$, $p = 0.010$; $r_S = 0.37$, $p = 0.007$] and AT-IR [$r_S = 0.36$, $p = 0.010$; $r_S = 0.37$, $p = 0.008$]) as well as with basal insulin ($r_S = 0.3$, $p = 0.005$ and $r_S = 0.34$, $p = 0.013$) and CP levels ($r_S = 0.51$, $p < 0.001$; $r_S = 0.55$, $p < 0.001$). On the opposite, sCD163 levels did not correlate with insulin levels but increased proportionally with adipo-IR (both Lipo-IR [$r_S = 0.28$, $p = 0.05$] and AT-IR [$r_S = 0.30$, $p = 0.032$]). Concerning the ability to discriminate hepatic fibrosis, CP and PRO-C6 levels were able to distinguish F0/F1 from F2 ($p = 0.013$; $p = 0.05$, respectively) while PRO-C3 and sCD163 levels discriminated F2 from F3/F4 ($p = 0.009$; $p = 0.002$, respectively). By biomarkers combination, the best performance for the identification of F3/F4 was obtained with CP and sCD163 with an area under the receiver operating curve (AUROC) of 0.91 (PPV = 83%; NPV = 91%).
Conclusion: In non-diabetic patients with NAFLD, the combination between CP and sCD163 provides the best performance for the assessment of severe fibrosis (F3/F4) yielding both a high positive and negative predictive value.
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FRI012

Comparison of diagnostic accuracy of magnetic resonance ideal-iq sequence and controlled attenuation parameter for detecting liver steatosis

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Background and Aims: It is well known that quantitative detecting liver steatosis is an essential step before treating Non-alcoholic Fatty Liver Disease (NAFLD). Magnetic resonance iterative decomposition of water and fat with Echo asymmetry and the Least Squares Estimation Quantification sequence (MR IDEAL-IQ) and Controlled Attenuation Parameter (CAP) are two noninvasive methods for quantitative detecting liver steatosis. No data reported that whether MR IDEAL-IQ or CAP is more accurate for detecting liver steatosis in NAFLD patients. So, the aim of this study was to compare the diagnostic accuracy of MR IDEAL-IQ sequence and CAP for detecting liver steatosis in NAFLD patients.
Method: One hundred thirty four patients with biopsy-proven NAFLD from Octorber 2016 to November 2019 were enrolled in this study and all of them were performed with MR IDEAL-IQ and CAP at the same period. Steatosis grade was defined according to the percentage of affected hepatocytes: S1 5–33%, S2 34–66%, S3 >67%. Area under receiver-operator curve (AUC) was used to calculate the diagnostic accuracy of these above two noninvasive tests.

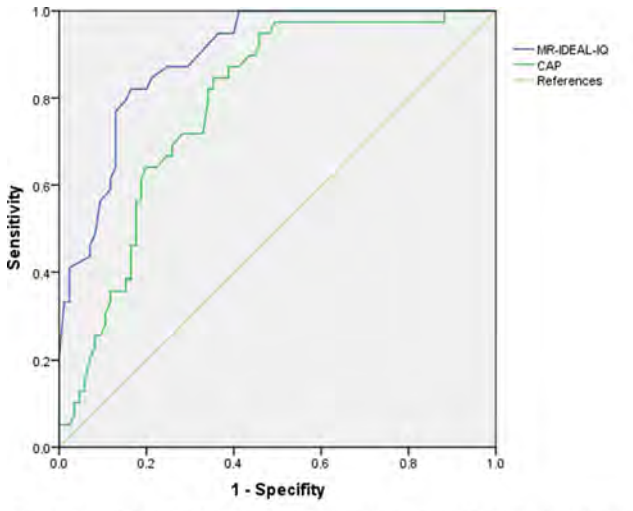

Fig.1 RCO curves for MR-IDEAL-IQ and CAP in detecting liver steatosis S≥3 in NAFLD patients

Results: Among the 134 NAFLD patients, 36, 52, 46 patients showed S1, S2, S3 respectively. The summary AUROC values using MR IDEAL-IQ and CAP for detecting steatosis $S \geq 2$ were 0.900 vs. 0.845 ($P = 0.229$) and $S \geq 3$ were 0.895vs. 0.785 ($P = 0.025$), respectively. The pooled sensitivity and specificity using CAP for the diagnosis of steatosis $S \geq 2$ and $S \geq 3$ were 71.4% and 87.9%, 84.6% and 64.7%, respectively. The pooled sensitivity and specificity using MR IDEAL-IQ for the diagnosis of steatosis $S \geq 2$ and $S \geq 3$ were 79.1% and 87.9%, 82.1% and 83.5%, respectively.

Conclusion: MR IDEAL-IQ is more accurate than CAP in diagnosing liver steatosis in patients with NAFLD, especially in diagnosing steatosis S ≥ 3.

FRI013

MACK-3: an accurate blood test for the diagnosis of fibrotic NASH and a candidate biomarker to monitor disease progression

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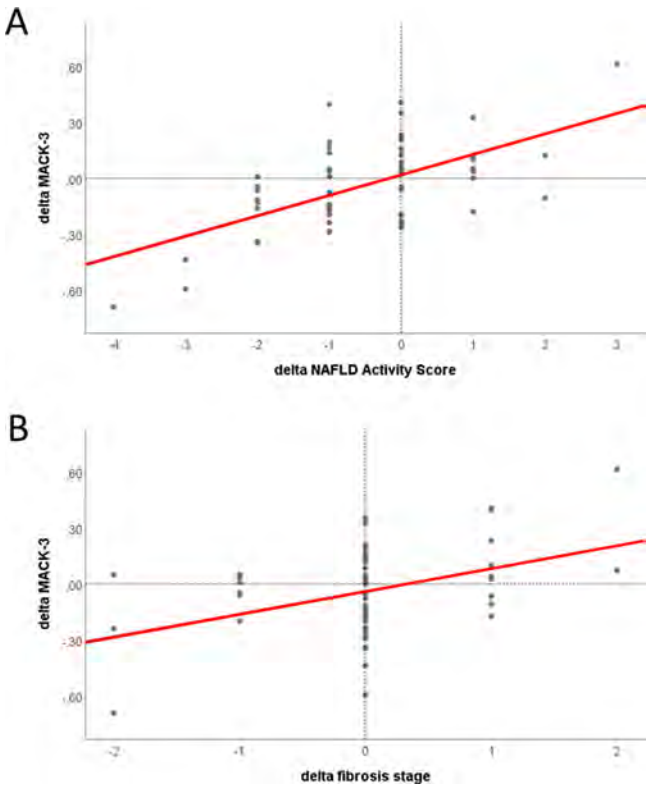
Background and Aims: MACK-3 is a blood test combining AST, HOMA and CK18 for the diagnosis of fibrotic NASH (NASH + NAS ≥ 4 + F ≥ 2), which is the inclusion criteria in NASH therapeutic trials. We aimed to validate the accuracy of MACK-3 in NAFLD.

Method: Cross-sectional study: 152 biopsy-proven NAFLD patients were prospectively included in our centre. Liver biopsies were scored by an expert pathologist using the NASH CRN classification. MACK-3 thresholds to rule-out and rule-in fibrotic NASH were, respectively, <0.135 and >0.549 (PMID 29577364). Longitudinal study: 57 additional patients with paired liver biopsies were retrospectively recruited to evaluate the ability of MACK-3 to monitor disease evolution.



Results: Cross sectional study. Mean age was 57.8 ± 11.4, male gender: 61%, BMI: 33.4 ± 6.2 kg/m^2, diabetes: 48%, fibrotic NASH: 41%. AUROC of MACK-3 for fibrotic NASH was 0.80 ± 0.04. At the lowest MACK-3 threshold (<0.135), sensitivity was 95% and negative predictive value was 93%. At the highest threshold (>0.549), specificity was 87% and positive predictive value was 68%. Among the 12 patients with false-positive result, 3 had advanced F3-4 fibrosis, 1 had NASH + F2, 2 had ballooning + F2, and 2 had NASH + NAS4. Longitudinal study: At baseline, 63% of patients had fibrotic NASH, mean NAFLD activity score (NAS) was 4.5 ± 1.3, and fibrosis stage were: F1: 16%, F2: 30%, F3: 46%, F4: 9%. Median follow-up was 2.5 years (1st quartile: 1.7; 3rd quartile: 4.7). The evolution of MACK-3 well correlated with the evolution of NAS (Rs = 0.48, p < 0.001; Figure A) and with the evolution of fibrosis stage (Rs = 0.31, p < 0.001; Figure B).

Conclusion: MACK-3 is an accurate blood test for the diagnosis of fibrotic NASH. It can be used to select patients for therapeutic trials and, once the new drugs for NASH will be approved, to identify patients who need to be treated in clinical practice. Because it well correlates with the evolution of liver lesions, MACK-3 is a candidate biomarker to monitor disease progression and assess treatment response.

FRI014

Diagnostic performance of three non-invasive fibrosis scores (Hepamet, FIB-4, NALFD score) on NAFLD in a mixed Latin American population

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Background and Aims: Several non-invasive scoring systems have been developed and validated to predict the risk of significant fibrosis in nonalcoholic fatty liver disease (NAFLD) in different scenarios over the world. However, it is scarce in Latin America and needs better validation in different countries in this region. Our aim was to evaluate the performance of three non- invasive fibrosis scores [Hepamet Fibrosis Score, Fibrosis-4 (FIB-4) and NAFLD Fibrosis Score (NFS)] in a mixed Latin America population.

Method: We conducted a retrospective cross-sectional study of 419 biopsy-proven NAFLD patients attending tertiary medical centers in Latin America. The diagnosis of NAFLD was based on histological criteria and fibrosis stages were determined according to using NASH CRN criteria. Clinical and laboratorial data were collected in the interval between three months before and three months after liver biopsy. According to liver biopsy results, histological fibrosis stages were classified as: significant fibrosis (F2-F3-F4); advanced fibrosis (F3-F4); and cirrhosis (F4). We calculated three non-invasive fibrosis scores: Hepamet, FIB-4 and NFS. Each score performance was evaluated through measurements of accuracy, sensibility, specificity, positive predictive value, negative predictive value and area under the ROC curve (AUROC).

Results: A total of patients with NAFLD were evaluated, being 240 (Brazil) 159 (Peru) 61 (Argentina). Among them the majority of patients were female (77%, 74%, 62,2%) respectively, with a mean age lower in Peru 38.96 (±10.38), than Brazil, 54.55 (±10.22), Argentina, 57.7 (+12.22). The mean body mass index (BMI) was 30.86 (±5.51) in Brazil, 38.36 (±6.07) in Peru, 30.80 (+4.66) in Argentina. The sample distribution of fibrosis stages on liver biopsies were as follows: Brazilian population: 17.1% F0, 38.8% F1, 9.1% F2, 26.8% F3 and 8% F4;

Peru population 55.3% F0, 18.2% F1, 1.2% F2, 21.3% F3 and 3.7% F4; Argentina population 27.8% F0, 36% F1, 22.9% F2, 8.1% F3 and 4.9% F4. The Hepamet AUROC for the detection of significant and advanced fibrosis was significantly higher than NFS in all three populations (Brazil, Peru and Argentina with $p = 0.03$; $p < 0,001$; $p = 0.004$, respectively and it was similar to FIB4 in all cohort.
Conclusion: The performance of both, FIB-4 and Hepamet scores, were satisfactory and similar to detect significant and advanced fibrosis in NAFLD Latin America population. This is the first study that validated Hepamet score in a mixed Latin America Population and compared with two validated scores.

FRI015
Identification of significant fibrosis in patients with non-alcoholic steatohepatitis using non-invasive tests: determination of optimal thresholds based on cross-sectional analyses of patients screened for a phase 3 randomised controlled trial
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Background and Aims: Few patients receive liver biopsies for diagnosis and staging of nonalcoholic steatohepatitis (NASH) in clinical practice. Where biopsy data are lacking, non-invasive tests (NITs) could identify patients with NASH fibrosis. However, whereas the performance and diagnostic cutoffs for NITs have been conditioned on fibrosis stages 3–4, there are limited data for stage ≥ F2. As NASH therapies in development seek to target people with ≥ F2, capacity to conduct real-world research in such patients is hindered. Using the screening database for entry into AURORA (Phase 3 trial to assess efficacy and safety of cenicriviroc for treatment of NASH fibrosis) we sought to determine the optimal thresholds on NITs for identifying significant fibrosis.
Method: The AURORA screening database included 2056 subjects with NASH who underwent screening liver biopsy and 3 NITs: FIB-4, NFS, and APRI. Liver biopsy was the gold standard and subjects were dichotomised as significant (NASH Clinical Research Network [CRN] F2-F4) or non-significant (NASH CRN F0-F1) fibrosis. Receiver operating characteristic (ROC) curves determined thresholds based on 3 NITs. The predictive accuracy of each NIT was evaluated using logistic regression. We selected 2 thresholds to maximise classification accuracy: a low threshold below which subjects were unlikely to have significant fibrosis (optimised for sensitivity ≥ 90%) and a high threshold above which subjects were likely to have significant fibrosis (optimised for specificity ≥ 90%).

Test	Cut-off	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Total (n)
FIB-4	≥1.79	31	91	34	90	488
	≤0.62	93	21	55	75	223
APRI	≥0.8	27	92	33	90	447
	≤0.2	96	12	55	74	155

Results: Distribution of subjects by fibrosis stage was F0 = 118 (6%), F1 = 459 (22%), F2 = 605 (29%), F3 = 765 (37%), F4 = 109 (5%). Area under the ROCs to discriminate significant fibrosis were acceptable for FIB-4 (0.71; 95% CI: 0.68–0.73) and APRI (0.69; 95% CI: 0.66–0.71). The thresholds determined on FIB-4 and APRI were ≥ 1.79 and ≥ 0.8 (likely to have significant fibrosis) and ≤ 0.62 and ≤ 0.2 (unlikely to have significant fibrosis), respectively (see Table).
Conclusion: This study is the first to identify optimal thresholds for NITs to identify significant fibrosis among NASH patients. FIB-4 and APRI can be used to identify significant fibrosis with an acceptable level of accuracy. Future research using other clinical trial and real-world cohorts should be conducted to further validate these results.
Editorial assistance by Complete HealthVizion.

FRI016
Patients with non-alcoholic fatty liver disease referred from primary care have a significant serum fibrosis marker and liver stiffness measurement discordance
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Background and Aims: The utilisation of serum and imaging biomarkers for diagnosis of liver fibrosis in non-alcoholic fatty liver disease (NAFLD) has increased. Understanding the concordance of serum fibrosis markers and Transient Elastography (TE) may help further optimise primary care referral pathways. In NAFLD this has had limited study. We present analysis from our primary care NAFLD algorithm of factors associated with serum fibrosis marker and TE concordance.
Method: A primary care NAFLD stratification pathway introduced by Oxford University Hospitals NHS Foundation Trust and Oxfordshire Clinical Commissioning Group was established in November 2017. Investigations are requested electronically by primary care. Patients with high risk FIB-4 (>2.67), or intermediate FIB-4 (1.30–2.67) with elevated ELF score (>= 9.5) are referred to a specialist Metabolic liver clinic. Patients aged <35 years directly undergo ELF testing, with a high risk threshold of >= 9.0. TE is performed routinely in clinic. Liver stiffness measurement (LSM)>= 8 kilopascals (kPa) is considered indicative of significant fibrosis. Results were considered concordant if patients with high risk FIB-4 or ELF scores had LSM>=8 kPa, and discordant if <8 kPa. Factors associated with biomarker concordance were assessed.
Results: Between November 2017 and May 2019, 670 patients were investigated on the pathway. Of 139 referred to liver clinic (110 with high risk ELF score and 29 with high risk FIB-4), valid LSM was obtained in 119 patients. Elevated LSM results were seen in 63.4% of patients with high FIB-4 and 56% of patients with high ELF. With a revised ELF threshold of 10, 54.2% of patients had elevated LSM. Overall, 28 patients with concordant results underwent liver biopsy; >=F3 fibrosis was seen in 17 (60.7%). Only 4 patients with discordant results underwent liver biopsy, of whom 1 (25%) had >=F3 fibrosis. Diagnoses of advanced fibrosis and cirrhosis were given in 54.3% and 31.4% of patients with concordant results, but only 1 patient (2%) with discordant results. Patients with concordant results were more likely to have type 2 diabetes (50.7% vs. 14%; $p < 0.01$) or obesity (72.6% vs. 51.1%; $p = 0.02$). No factors, including joint disease or Age, were associated with discordant results.
Conclusion: A significant percentage of NAFLD patients with elevated FIB-4 or ELF scores referred from primary care have normal liver stiffness. This impacted on both liver biopsy utilization, and diagnosis of advanced fibrosis and cirrhosis. No factors could be identified to predict discordant serum and LSM results.

FRI017

Comparison of point-shear wave elastography (ElastPQ) and fibroscan transient elastography (F-TE) for liver fibrosis staging in patients with NAFLD

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Background and Aims: ElastPQ is a point shear wave elastography technique used to non-invasively assess liver fibrosis. We compared liver stiffness measured by both ElastPQ and Fibroscan Transient Elastography (F-TE) in a cohort of consecutive patients with NAFLD. We further evaluated the performance of ElastPQ in a subgroup of patients with available liver histology.

Method: Anthropometric parameters (weight, height, BMI and waist circumference (WC)) were measured on the same day of routine bloods tests. Elastography measurements were carried out using F-TE (Echosens, Paris) and ElastPQ (Affiniti 70G, Philips) in all recruited patients. We considered liver biopsies performed within one year of the non-invasive assessment.

Results: We enrolled 546 consecutive patients with NAFLD, mean age 56 ± 13 y, BMI 31.9 ± 6.4 kg/m^2, WC 107.6 ± 15.5 cm, 57% male; 42% had diabetes, 55% hypertension, 72% hyperlipidaemia.

ElastPQ showed a good correlation with F-TE (CCC Lin's = 0.91, 95%CI 0.90–0.93, p < 0.001), which was better for mild and moderate stages of fibrosis. A ≥ 2 kPa difference between the two techniques was found in 128 (23.4%) patients. On multivariate analysis, the only independent predictor of such difference was F-TE ≥ 10 kPa (OR: 6.93, 95% CI 4.04–11.90, p < 0.001).

	ElastPQ				FIBROSCAN				
	Cut-off (kPa)	Sensitivity (%)	Specificity (%)	AUC	Cut-off (kPa)	Sensitivity (%)	Specificity (%)	AUC	P value*
F ≥ 2	7.8	77	77	0.80	7.8	84	78	0.82	0.515
F ≥ 3	8.9	81	76	0.86	9.8	78	76	0.83	0.741
F 4	13.4	90	90	0.97	13.5	84	85	0.91	0.637

In the subgroup of 142 patients with available histology, the distribution of fibrosis was as follow: F0 = 20 (14%), F1 = 48 (34%), F2 = 26 (18%), F3 = 29 (21%), F4 = 19 (13%).

The optimal cut-off values of ElastPQ for individual stages of fibrosis were similar to those obtained for F-TE. ElastPQ showed the same diagnostic performance of F-TE in all stages of fibrosis (Table 1).

Conclusion: ElastPQ and F-TE showed an excellent correlation in patients with NAFLD, which is better for low values of liver stiffness. The optimal cut-off values of ElastPQ are similar to those of F-TE for individual stages of fibrosis. ElastPQ has similar diagnostic accuracy to F-TE for all stages of fibrosis. ElastPQ, as well as F-TE, performs better to diagnose the presence of liver cirrhosis.

FRI018

Digital image analysis for quantitative evaluation of fibrosis, steatosis, inflammation and iron overload in patients with non-alcoholic fatty liver disease

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Background and Aims: Liver biopsy is frequently used for the assessment of liver disease severity in patients with non-alcoholic fatty liver disease (NAFLD). Interpretation of biopsies is based on semiquantitative scoring systems, carrying a risk of misclassification. In the present study, we evaluate the relationship between biopsy grading scores and the corresponding amount of collagen, fat, inflammation and iron quantified by computer-assisted digital image analysis (DIA).

Method: Prospective, multicenter, comparative study of digital pathology for the quantification of histologic features in liver biopsies of subjects with suspected-NAFLD. Samples were stained with: Picrosirius red for fibrosis detection, Perl's stain for iron, immunohistochemistry with adipophilin for fat and CD45 for inflammation. Grading scores included: METAVIR for fibrosis, Nonalcoholic Steatohepatitis Clinical Research Network (NASH-CRN) for steatosis and inflammation, and Deugnier for iron deposits. Stained tissue sections were scanned (Ventana iScan HT®) for DIA. Quantitative variables were expressed as proportional areas (%) of collagen (CPA); fat (FPA); inflammation (IPA); and iron (FePA). Statistical analysis was performed using ANOVA test for comparisons of DIA data among corresponding semiquantitative groups (METAVIR, NASH-CRN); and Spearman's co-efficient for correlation of quantitative data (Deugnier).

Results: The study included 80 patients (58% women; median age, 55 years; range, 48–63) with a median body mass index of 29 (range, 24–32). Median length and portal tracts of biopsies were 21 mm (range, 17–24) and 10 (range, 7–13) respectively. CPA values increased significantly with fibrosis stages (7.4 ± 1.9, 8.7 ± 1.3, 8.8 ± 1.3, 10.1 ± 2.4 and 13.5 ± 2.3, F0-F4 respectively, p < 0.001). FPA values increased significantly with steatosis stages (3.5 ± 2.2, 9.1 ± 5.0, 13.0 ± 4.2, and 20.3 ± 9.4, S0-S3 respectively, p < 0.001). IPA values were significantly different between inflammation stages (5.1 ± 1.7, 6.2 ± 1.8, 7.2 ± 3.3, and 9.9 ± 4.3, I0-I3 respectively p = 0,001). FePA correlated significantly with Deugnier's score (r = 0.84; p < 0.001). Results are represented in Figure 1.

Conclusion: Computational DIA provides an accurate evaluation of histological features in NAFLD, showing a high correlation with current semiquantitative scores. DIA measurements should be now validated towards in vivo non-invasive biomarkers.

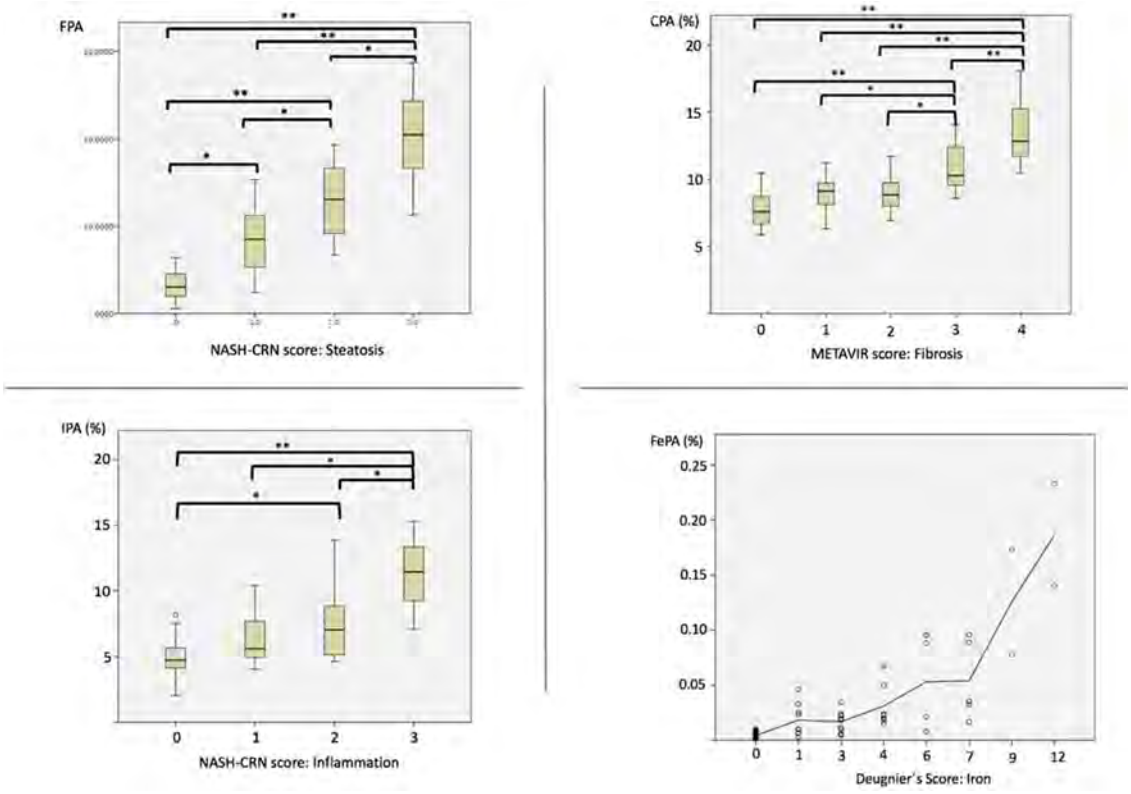

Figure: (abstract: FRI018): Distribution of DIA data across semiquantitative histologic scores.

FRI020

Metabolomics composite biomarkers selected by machine learning predicts NASH

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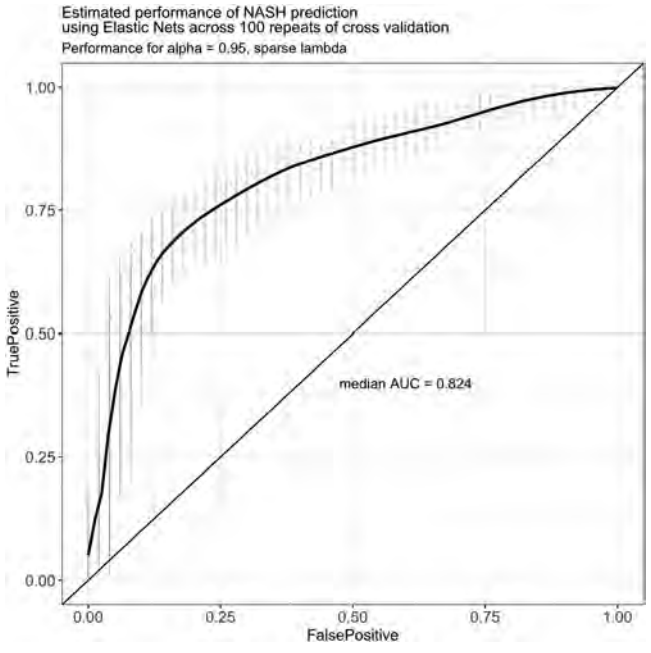
Background and Aims: Non-alcoholic fatty liver disease (NAFLD) affect about 25% of the US population. Additionally, 1.5–6.5% have the progressive form of NAFLD or non-alcoholic steatohepatitis (NASH). Currently the diagnosis of NASH requires a liver biopsy and a serum based non-invasive test will be highly desirable. Here we use broad metabolic profiling of biopsy-proven NAFLD patients' serum samples to discover potential metabolite biomarkers of NASH and develop predictive composite biomarkers to diagnose it.

Method: Serum samples were obtained from 100 biopsy-proven NASH (F0-F4) and 50 NAFLD patients without NASH (simple steatosis or NAFL). We used liquid-chromatography mass-spectrometry (LCMS) to characterize metabolite fluorescent intensities. For 235 metabolites detected in >50% of the samples, we log2 and quantile normalized the data. Controlling for plate, age, sex, and diabetes, we applied limma to model metabolite associations with all NASH (F0-F4) vs NAFL, NASH with significant fibrosis (F2-F4) vs NAFL and early NASH (F0-F1), advanced NASH (F3-F4) vs NAFL and early NASH, and NASH F4 vs NASH F3 with Benjamini-Hockberg multiple testing correction. We also used the glmnet package in R to conduct the Elastic Nets algorithm with cross-validation to reduce the number of biomarkers and clinical predictors, and obtain two models to predict all NASH and advanced fibrosis. We applied repeated loops of cross-validation to predict out-of-sample performance of our selected models by area under the curve (AUC) of the receiver operating characteristic (ROC).



Results: We detect substantial signatures of metabolites associated with NASH (52 for adjusted p < 0.1) and advanced stages of NASH. In particular, we see strong down-regulation of many dicarboxylic acids and broad upregulation of secondary bile acids. Applying elastic nets with cross-validation, we find that 12 metabolites plus patient diabetes status classify NASH vs NAFL patients with predicted out-of-sample power AUC = 0.824. In addition to dicarboxylic and bile acids, predictors include lipid and microbiome-derived metabolites.
Conclusion: Using broad metabolomic profiling, we have discovered many potential biomarkers associated with NASH and advanced NASH. In particular, we have strong predicted performance to use composite metabolic biomarkers to distinguish NASH patients from those with NAFL, an unmet clinical need for NASH diagnostics. This should be validated in independent cohorts.

FRI021

Diagnostic accuracy of acoustic radiation force impulse elastography for the staging of hepatic fibrosis in non-alcoholic fatty liver disease: a systematic review and meta-analysis

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease in the world, affecting almost one-third of the population in Western countries. There is an unmet need for non-invasive biomarkers to replace liver biopsy and ultrasound-based elastography techniques have shown promising results. The aim of this systematic review and meta-analysis was to evaluate the diagnostic performance of acoustic radiation force impulse (ARFI) elastography for staging hepatic fibrosis in patients with NAFLD.
Method: An electronic search of PubMED, EMBASE and Cochrane Library was conducted for full-text papers and conference abstracts examining the diagnostic test accuracy of ARFI. Studies reporting on adults with biopsy-proven NAFLD using the NASH CRN histological scoring system and ARFI within 6 months of biopsy were included. Contingency tables for each fibrosis group were constructed from reported diagnostic accuracy for each study. Summary sensitivities, specificities and area under the receiver operating characteristic curve (sAUROC) were produced using a bivariate model. Risk of bias was assessed using the QUADAS-2 tool.
Results: Nine studies (n = 1218 patients, 52% male) provided sufficient data for meta-analysis. Two studies were conducted in France, the USA and South Korea, respectively, one in Germany and one in Romania. Seven studies reported the proportion of obese participants (mean prevalence 63%) and 6 studies reported the proportion of patients with diabetes (mean prevalence 39%). Experienced radiologists performed ARFI using either Siemens Acuson S2000 or S3000 with a mean technical failure rate of 8%. Summary statistics for diagnosing stages of fibrosis are given in the accompanying table. All 9 studies were judged as having high risk of bias in the index test domain as none of them used predefined cut-off values or included patients with failed or unreliable test for diagnostic accuracy analysis.

Target condition	Number of patients	Prevalence, %	Number of studies	Cut-off range, kPa	sAUROC	Sensitivity, %	Specificity, %
F ≥ 1	249	49	3	1.11–1.81	0.77	60	76
F ≥ 2	641	58	6	1.17–1.81	0.89	77	90
F ≥ 3	1170	29	8	1.34–4.24	0.93	81	89
F = 4	720	16	6	1.50–2.54	0.93	73	92

Conclusion: In patients where liver stiffness can be successfully measured using ARFI, the test has excellent diagnostic accuracy for fibrosis. However, "intention to diagnose" analyses and validation of pre-specified cut-offs are lacking from the literature and these areas should be the focus of future studies.

FRI022

Three is enough: optimization of regions of interest selection for accurate estimation of proton density fat fraction in liver from magnetic resonance images

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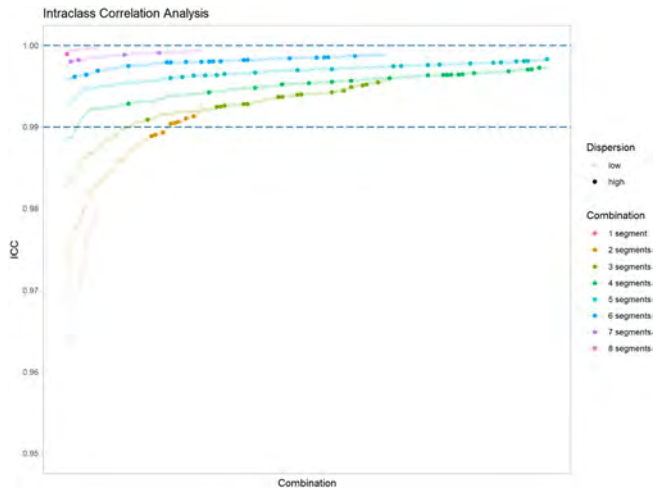
Background and Aims: Proton Density Fat Fraction (PDFF) measured by magnetic resonance imaging (MRI) is now widely accepted as a biomarker for liver fat fraction in non-alcoholic fatty liver disease (NAFLD) and steato-hepatitis (NASH), correlating highly with both MR spectroscopy and histology of liver biopsies. Here we demonstrate that average PDFF from a subset of widely dispersed regions of interest (ROI) correlates highly with a set of ROIs placed in each of the 9 Couinaud segments of the liver. We propose that PDFF based on the average of a subset number of ROIs with a high dispersion, provides an accurate estimate of liver fat fraction that compares favourably with more complicated, time-consuming and artefact-prone methods.
Method: PDFF maps (N = 96) were randomly extracted from an anonymous data registry of clinical trials for NAFLD. Liver PDFF maps were generated using the method of Zhong, et al. (2014), to estimate water and fat components. A 3 cm^2 ROI was placed in each Couinaud segment and average PDFF was then calculated over these 9 ROIs and over all combination of 1 to 8 ROIs. A dispersion score was constructed to represent the physical separation between ROIs in each set. Average PDFF values for each combination of ROIs was compared to the value calculated for all 9 ROIs using statistical measures of intraclass correlation coefficient (ICC), absolute error (AE) and limits of agreement (LOA). These statistics were examined as a function of dispersion score.
Results: For ICC, AE and LOA the average PDFF value computed from more ROIs leads to increased correlation with the 9 ROIs strategy. ROI combinations with higher dispersion score (best 25% combination for each number of ROIs selected) also results in higher, stable values of ICC, AE and LOA metrics (except for 2 ROIs selection): ICC > 0.99, AE < 0.9% and LOA < 2.7%.



Conclusion: Close agreement between average liver PDFF values suggests that selecting at least 3 ROIs with the greatest dispersion over the Couinaud segments produces a valid and reliable alternative to using 9 ROIs. Fewer ROIs can be placed more efficiently and reliably across the liver, taking care of avoiding vessels and any potential artefacts, compared to defining 9 ROIs in the Couinaud segments. We demonstrate quantitatively for the first time, that more complex and time-intensive approaches to liver segmentation and ROI selection yield little improvement in the quality of the resulting PDFF measurements compared with 3 or 4 widely dispersed ROIs.

FRI023

Diagnostic accuracy of magnetic resonance elastography for the staging of fibrosis and diagnosis of steatohepatitis in patients with non-alcoholic fatty liver disease: a systematic review and meta-analysis

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in Western countries. Histology is used for diagnosis and follow-up but has limitations. There is a need for non-invasive biomarkers to replace biopsy, therefore we evaluated the diagnostic accuracy of magnetic resonance elastography (MRE) for staging fibrosis and diagnosing non-alcoholic steatohepatitis (NASH) in NAFLD patients.
Methods: An electronic search of PubMED, EMBASE and Cochrane Library was conducted for full-text papers and conference abstracts examining the diagnostic test accuracy of 2D MRE. Studies reporting on adults with biopsy-proven NAFLD using the NASH CRN histological scoring system and MRE within 3 months of biopsy were included. Contingency tables were reconstructed from reported diagnostic accuracy measures. Risk of bias was assessed using the QUADAS-2 tool.
Results: Ten studies (one conference abstract and nine research papers, n = 990 patients, 40% male) provided sufficient data for meta-analysis. Eight studies were conducted in the USA, one in Japan and one in Brazil; only one study reported the proportion of obese participants (57%), although nine studies reported a mean or median BMI > 30 kg/m^2, and seven studies reported on patients with diabetes (average prevalence 38%). Nine studies did not use predefined cut-off values. Six studies did not report on the technical failure rates and none of the studies reported on rates of subjects excluded due to contra-indications to MR. Summary statistics for diagnosing stages of fibrosis and NASH are given in the accompanying table. Only one study, that used predefined cut-offs, was scored as having low risk of bias in all four domains (patient selection, index test, reference standard, flow and timing). The rest of the studies had high risk of bias in at least one domain.

Target condition	Total number of patients	Prevalence, %	Number of studies	Cut-off range, kPa	sAUROC	Sensitivity, %	Specificity, %
F ≥ 1	536	58	5	2.50–3.14	0.861	68.6	86.3
F ≥ 2	536	30	5	2.86–4.14	0.901	77.2	90.1
F ≥ 3	932	19	9	2.99–4.80	0.925	82.9	89.6
F = 4	536	8	5	3.35–6.70	0.916	83.5	90.8
NASH	376	69	4	2.53–3.26	0.826	65.3	82.4

Conclusion: When MRE could be successfully performed the test had a high diagnostic accuracy for fibrosis. Data on intention to diagnose analysis and validation of pre-specified cut-offs are lacking from the literature and should be the focus of future prospective studies. Further evaluation is also needed in specific populations especially those with obesity.

FRI024

Investigation of a composite imaging biomarker for identification of non-alcoholic steatohepatitis (NASH) patients in a Japanese population

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Background and Aims: NASH pathogenesis is complex and composite biomarkers can improve identification of patients who are at risk of poor clinical outcomes. Liver*MultiScan*® uses multiparametric MRI to measure proton density fat fraction (PDFF) and iron-corrected T1 (cT1). PDFF quantifies hepatic steatosis while cT1 correlates with key histopathological features of NASH – ballooning, inflammation and fibrosis, and predicts clinical outcomes in patients with chronic liver disease. Herein, we report the performance of cT1 and PDFF in composite with non-imaging biomarkers, for the stratification of patients with suspected NASH in a prospective Japanese study cohort.
Method: Patients suspected of NASH underwent a 15-minute, contrast-free multiparametric MRI (Liver*MultiScan*, Perspectum Diagnostics). Liver biopsy was assessed using the NAFLD activity score (NAS) with NASH diagnosed as NAS ≥ 4 (ballooning ≥ 1, inflammation ≥ 1); fibrosis stage was assessed according to the Kleiner-Brunt criteria (F0-F4). The ability of the biomarkers to identify patients with (i) NASH and (ii) high-risk NASH (NAS ≥ 4 and F ≥ 2) was evaluated using area under receiver operating curve (AUROC) analysis, with logistic regression used to combine biomarkers.

Results: 97 patients were screened and underwent liver biopsy. Mean age was 60.1 years [28–82], mean BMI (±SD) was 29.0 (±4.7) kg/m^2, 38% were female and 54% had NASH. 23% were F1, 25% F2, 33% F3, and 16% F4 fibrosis; 45% were high-risk NASH. cT1 correlated with histological grading of fibrosis ($r_s = 0.34$, $p < 0.001$), inflammation ($r_s = 0.47$, $p < 0.001$), and ballooning ($r_s = 0.45$, $p < 0.001$); PDFF correlated with histological grading of steatosis ($r_s = 0.68$, $p < 0.001$). For identifying NASH, respective AUROCs for cT1 and PDFF were 0.76 (95% CI 0.66–0.86) and 0.77 (95% CI 0.68–0.87). For identifying high-risk NASH, respective AUROCs for cT1 and PDFF were 0.72 (95% CI 0.61–0.82) and 0.66 (95% CI 0.56–0.77). The optimal combination of cT1, PDFF, age and AST yielded a higher AUROC of 0.85 (95% CI 0.77–0.93) and 0.79 (95% CI 0.70–0.88) for identifying NASH and high-risk NASH, respectively (Figure 1).

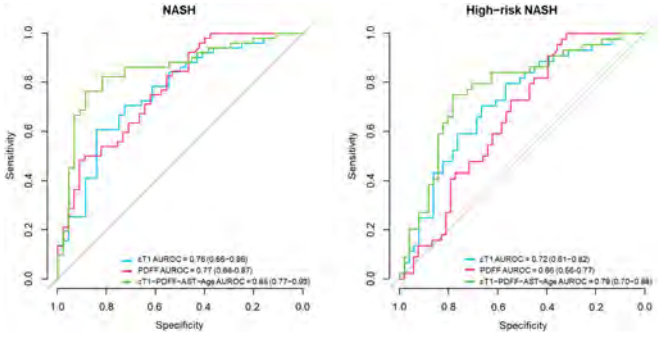

Figure 1: ROC curves to discriminate patients with NASH (left), and high-risk NASH (right).

Conclusion: In Japanese patients, cT1 outperformed PDFF for identification of high-risk NASH. Performance of cT1 was enhanced in combination with PDFF, age and AST for identification of NASH patients as well as those with significant fibrosis.

FRI025

External validation of hepatic estimated steatosis index using magnetic resonance image

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Background and Aims: NAFLD is the most common cause of chronic liver disease. The gold standard for determining hepatic fat deposition is a liver biopsy, but it is invasive and has the disadvantages of limited sampling and high cost. Therefore, in real clinical world, hepatic sterilization is assessed using ultrasound or estimated hepatic steatosis formulae. However, the currently used calculated steatosis formula uses a ultrasound which has low sensitivity and misses patients in the gray zone. Therefore, we compared the diagnostic performance of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of conventional estimated hepatic steatosis formulas through MRI-PDFF which is used as gold standard with liver biopsy.
Method: The subjects of this study were those aged 18 years or older who visited Gangbuk Samsung Health Examination Center (Seoul, Suwon) from January 2015 to May 2018 and underwent intrahepatic fat measurement using MRI test. MRI was used 1.5 T MRI without contrast media and hepatic fat fraction percentage was measured by chemical shift technique. Diagnostic performances were compared using analytical methods such as Mann-whitney test, Independent t-test, Chi-square test, Spearman correlation, logistic regression, and AUROC.
Results: Among 1301 patients, ultrasound diagnosed NAFLD was 25.5% (549/2149), and MRI diagnosed NAFLD was 18.2% (392/2149). The sensitivity of fatty liver diagnosis using ultrasound was 71.9% (282/392), specificity was 67.1% (549/817), positive predictive value (PPV) was 51.1% (281/549), and negative predictive value (NPV) was 81.9% (549/670). AUROC of fatty Liver index (FLI), Hepatic Steatosis index (HSI), and NAFLD liver fat score were 0.68, 0.70, 0.72, respectively. NAFLD liver fat score showed the best diagnostic ability, but overall AUROC was low. Intermediate zones between high cut off and low cut off were the lowest in FLI (28.9%) and 43.3% and 50% in HSI and ZJU, respectively.
Conclusion: The performance of fatty liver diagnosis using the estimated hepatic steatosis formulae was slightly lower, ranging from 0.68 to 0.72. There is a need for further development of non-invasive diagnostic methods for the diagnosis of fatty liver.

FRI026

The prevalence of non-alcoholic fatty liver disease in type 2 diabetes mellitus

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Background and Aims: Non-Alcoholic Fatty Liver Disease (NAFLD) is becoming an important cause for chronic liver disease worldwide and is one of the leading causes for hepatocellular carcinoma. In patients with type 2 diabetes mellitus (T2DM), NAFLD is reaching epidemic dimensions. Insulin resistance is a key contributor to the development of NAFLD and T2DM. Therefore, patients with T2DM have a higher chance of developing NAFLD. Nevertheless, little to no epidemiologic data is available about the presence of NALFD in T2DM patients. Our aim is to determine the prevalence of NAFLD and fibrosis in a cohort of T2DM patients followed at Ziekenhuis Oost-Limburg (ZOL), Belgium.
Method: In a retrospective, cohort study in ZOL, a large regional hospital in Limburg, Belgium the prevalence of NAFLD was determined by means of non-invasive score calculations in 1,000 of 2,910 T2DM patients. The Fibrosis-4 (FIB-4) score was used to determine liver fibrosis and the Fatty Liver Index (FLI) to determine the fat content of the liver.
Results: Thirty-seven of the 1,000 analysed patients were excluded due to reported other liver diseases, a history of bariatric surgery, or age 35 years or younger. In 218/972 (22.4%) T2DM patients, values for the FLI score were available and 525/972 (54.0%) patients had values for the FIB-4 score. In relation to steatosis, little to no steatosis was found in 14/218 (6.4%) patients, a moderate amount of liver fat was found in 31/218 (14.2%) patients, and a serious amount of liver fat in 173/218 (79.4%) of the cases. In relation to fibrosis, 63/525 (12.0%) patients had liver cirrhosis, 125/525 (23.8%) had significant fibrosis, and 337/525 (64.2%) had little to no fibrosis.

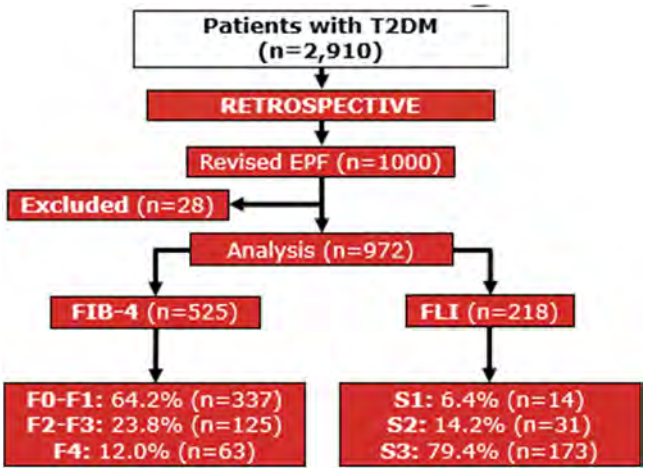

Figure 1: **The prevalence of NAFLD in the total cohort of T2DM patients followed at ZOL**. S1: little to no steatosis, S2: mild steatosis, S3: severe steatosis, F0-F1: little to no fibrosis, F2-F3: significant fibrosis and F4: cirrhosis, EPF: electronic patient file, T2DM: type 2 diabetes mellitus, FIB-4: fibrosis-4 score, FLI: fatty liver index.

Conclusion: One out of ten T2DM patients has evolved to liver cirrhosis. More than a quarter has significant fibrosis and are therefore eligible for anti-fibrotic/steatotic therapy. Four out of five patients has significant steatosis or NAFLD.

FRI027

Validation of interleukin-32 as a new circulating fatty liver biomarker

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Background and Aims: Efforts to manage nonalcoholic fatty liver disease (NAFLD) are limited by the absence of accurate noninvasive biomarkers. The I148M variant in *PNPLA3* is a major determinant of the development and progression of NAFLD associated with a distinct disease pathophysiology. Aim of the study was to identify novel candidate NAFLD biomarkers by examining the hepatic transcripts associated with severe NAFLD in obese individuals in patients stratified by the presence of the PNPLA3 I148M variant.

Method: Hepatic transcriptomic analyses were conducted in 125 liver-biopsied severely obese individuals. "Severe NAFLD" was defined as the presence of steatohepatitis, or NAS ≥ 4, or fibrosis stage ≥ 2. RNA was isolated from liver biopsies and sequenced (HiSeq4000). After reads alignment (STAR software) and count (RSEM), differential expression was investigated at gene (DESeq2) and pathway (GSEA) level. Plasma IL32 was measured in other 71 liver-biopsied obese patients (Biomarker cohort) by ELISA (R&D), in an independent validation cohort of 44 individuals with metabolic disorders in which steatosis was evaluated by coefficient attenuation parameter (CAP) and in a further validation cohort of 174 liver-biopsied patients at risk for NAFLD.

Results: Principal component analysis revealed that carriage of the PNPLA3 I148M variant was one of the most important determinant of transcriptome variability. Indeed, carriage of the variant highly correlated with the first two principal component of transcriptome variability ($p < 0.001$, both). Consistently, differential gene expression analysis revealed overexpression of inflammatory genes together with a downregulation of metabolic genes in PNPLA3 I148M carriers. Conversely, severe NAFLD patients overexpressed genes involved both in inflammatory response and oxidative metabolism. Importantly, IL32 showed the strongest association with severe NAFLD (adjusted $p = 1^{*}10^{-6}$).

In the biomarker cohort, plasma IL32 levels were associated with both NAFLD and severe NAFLD ($p < 0.01$ for both). In our first validation cohort ($n = 44$), circulating IL32 positively correlated with CAP value ($p = 0.03$). Importantly, in a further validation set of 174 liver-biopsied patients we confirmed serum IL32 association with both NAFLD ($p = 9^{*}10^{-5}$) and severe NAFLD ($p = 0.008$).

Conclusion: This work highlights PNPLA3 148M allele as the major determinant of transcriptome variability and IL32 as a novel potential biomarker for noninvasive NAFLD diagnosis.

FRI028

Simple non-invasive prediction of advanced fibrosis in NAFLD - a stepwise approach and external validation study to reduce indeterminates and biopsy

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Background and Aims: Advanced hepatic fibrosis predicts liver-related mortality in NAFLD. Simple Non-invasive Tests (NIT) designed to rule-in or rule-out advanced fibrosis in NAFLD are limited by 'indeterminate' (IND) results, necessitating liver biopsy. Our aim was to determine whether sequential or parallel combinations of serum-based NIT and elastography (VCTE) can accurately predict advanced NAFLD fibrosis (AF), reduce IND and misclassifications (MIS), and thus decrease need for liver biopsy.

Method: Biopsy-proven NAFLD patients were retrospectively identified between 2010–2018 from two Canadian tertiary centres to represent derivation and external validation cohorts for sequential algorithms. Cohorts were combined for parallel analysis. FIB-4, APRI, NFS, BARD, AST/ALT scores were calculated based on blood work performed within 6 months of biopsy. VCTE was available in $n = 172$, and liver stiffness measurement (LSM) ≤ 7.2 kPa was considered as F0-2. AF was defined as F3-4 fibrosis stages. Areas under the ROC curve (AUC) and weighted Obuchowski measures (OB) were determined for binary outcomes.

Table 1:

	Derivation					Validation				
Sequential NIT	Sens	Spec	AUC (OB)	IND	MIS	Sens	Spec	AUC (OB)	IND	MIS
FIB-4	0.66	0.94	0.83 (0.74)	27%	17%	0.88	0.61	0.81 (0.74)	34%	26%
NFS	0.64	0.90	0.78 (0.71)	25%	23%	0.64	0.85	0.78 (0.72)	40%	25%
FIB-4 + NFS	0.60	0.95	0.77 (0.71)	8%	20%	0.56	0.82	0.67 (0.65)	15%	30%
FIB-4 + VCTE	0.69	0.93	0.81 (0.72)	0%	17%	0.67	0.66	0.66 (0.64)	0%	34%
FIB-4 + NFS + VCTE	0.62	0.94	0.78 (0.71)	0%	20%	0.62	0.74	0.68 (0.64)	0%	31%

Results: 541 cases of NAFLD were identified (407 derivation, 134 validation). Characteristics of derivation/validation cohorts included: males 54%/59%; mean age 48.5/52.5 yrs; mean BMI 32.3/33.6; diabetes 30%/34%; AF 48%/43%. For single serum NITs, AUC for AF

were 0.70–0.83, and 0.68–0.81 for derivation and validation cohorts, with IND rates of 25%–39%, and 34%–45%. Concordance between FIB-4 and NFS for both cohorts was 71–73%. Sequential combinations of NIT reduced IND while maintaining diagnostic accuracy (Table 1). For the overall cohort, parallel FIB-4 + NFS had similar accuracy (AUC = 0.81) but was limited by a 38% IND rate. In our overall cohort, liver biopsy for AF was avoided in 27–30% of patients using sequential algorithms, representing an additional 6–9% biopsies avoided compared to using FIB4/NFS/VCTE alone.

Conclusion: Sequential combinations of NIT predict advanced fibrosis in NAFLD with good accuracy, while reducing IND. Use of sequential algorithms reduce need for liver biopsy compared to individual NIT. Parallel combined algorithms are limited by high rates of IND. In our tertiary cohorts, sequential FIB-4 + NFS performed with similar accuracy to VCTE-containing algorithms, and if validated in low prevalence cohorts, highlights potential use in resource-limited clinical settings as a means of risk stratification for advanced NAFLD fibrosis.

FRI029

Adherence to established process measures in the evaluation of hepatic steatosis on imaging in a large tertiary care network

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Background and Aims: Hepatic steatosis (HS) is a common finding on imaging studies. Clinical practice guidelines propose several process measures for risk stratification and referral of non-alcoholic fatty liver disease (NAFLD) cases. Adherence to process measure guidelines are not well known. We sought to assess rates of process measure completion among patients with a new imaging finding of HS in a large tertiary care network.

Method: Using natural language processing, we identified an inception cohort of patients aged 18–79 years with HS on abdominal imaging between 1/1 2015 and 12/31/2018. Using manual chart review, we excluded patients with known chronic liver disease (including NAFLD) and patients not receiving primary care at our institution (defined as no visits in the year prior to the imaging study). We assessed the following NASH risk factors: age > 50, persistent elevation in ALT, or 1+ metabolic syndrome (MetS) comorbidities; we calculate FIB-4 and NAFLD fibrosis scores (NFS) where possible. For FIB-4 and NFS, low risk was defined <1.3 or <−1.455 and high risk as >2.67 or >0.676, respectively. The primary outcomes were completion of the following process measures within one year of identifying HS: liver chemistry measurement, assessment of MetS comorbidities (hemoglobin A1C, HDL-C, triglycerides, and blood pressure), fibrosis risk assessment (NFS, FIB-4, vibration controlled transient elastography [VCTE], acoustic radiofrequency imaging [ARFI] or magnetic resonance elastography [MRE]) or referral to hepatology where appropriate.

Results: We identified 385 patients with new HS. 61% of imaging tests were ordered for non-liver-related indications and 48% by primary care physicians. Nearly all (95%) patients had >=1 NASH risk factor, and 14% were high risk for fibrosis using at least one risk score. 92% of patients had liver chemistries measured within 1 year of imaging, but only 48% of patients had a complete assessment for MetS. No provider documented calculation of a fibrosis risk score. Only 9% of patients (n = 35) underwent non-invasive testing for fibrosis (VCTE, ARFI or MRE). 16% (12/75) of patients classified as low risk on *both* scores were referred to hepatology, and only 13% (6/48) with >=1 high-risk score were referred to hepatology for further risk stratification or biopsy.

Conclusion: Significant room for improvement exists in the identification and evaluation of patients with IHS by imaging. These results highlight the need to redesign systems of care to facilitate guideline-recommended evaluation and referral among high-risk NAFLD patients.

FRI030

Value of FIB-4 and NAFLD fibrosis scores for screening of liver fibrosis in the general population

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Background: Serum biomarkers of liver fibrosis such as the fibrosis-4 (FIB-4) score and the NAFLD fibrosis score (NFS) have been proposed as first step for the identification of subjects with suspected liver fibrosis in primary care. These scores have a high negative predictive value (>90%), leaving more specific non-invasive tools such as transient elastography (TE) as second step. However, the diagnostic value of FIB-4 and NFS is mainly based on cohorts from secondary and tertiary care where the prevalence of fibrosis is high (20–30%). The performance of both tests for screening of the general population (with low fibrosis prevalence <5%) is unclear. Therefore we aimed to evaluate the bivariate relation between liver stiffness measurement (LSM), assessed using TE, vs. FIB-4 and NFS in the general population without known liver disease.

Patients and Methods: Data from a consortium-wide database of 4,255 adults (Age 53.53 (sd 12.11), 2,439 female (57.3%), BMI 27.1 (sd 5.16) without known liver disease who underwent screening for liver fibrosis with TE and NITs was included. The distributions of LSM, FIB-4 and NFS at different cutoffs were evaluated. LSM>8 kPa was chosen as cutoff for suspected advanced fibrosis, according to findings from recent studies. FIB-4 and NFS cutoffs below 1.3 and −1.45 were used for defining subjects at low-risk of having advanced fibrosis whereas cutoffs above 2.67 and 0.676 were used for defining high-risk subjects. Subjects with values in between were considered at intermediate risk.

Results: The mean FIB-4 score was 1.16(sd 0.59), NFS −2.04(sd 1.32), and LSM 4.91 kPa(sd 2.28). Out of 4,255 patients included, 235 (5.5%) patients had LSM >8 kPa. FIB-4 values were distributed as follows: <1.3 n = 2,733(68.3%), 1.3 < < 2.67 n = 1,198(29.9%) and >2.67 n = 69 (1.7%); NFS values were distributed as follows: <−1.45 n = 2,700 (68.5%), −1.45 < < 0.676 n = 1,168 (29.6%) and >0.676 n = 74 (1.9%). Among the 2,733 patients with FIB-4 < 1.3, 140 (5.1%) had LSM >8 kPa while among the 2,700 patients with NFS <−1.45, n = 104 (3.9%) had LSM >8 kPa. Among patients with FiB-4 >2,67 and NFS >0.676, 11 (15.9%) and 19 (25.7%) had LSM >8 KPa, respectively.

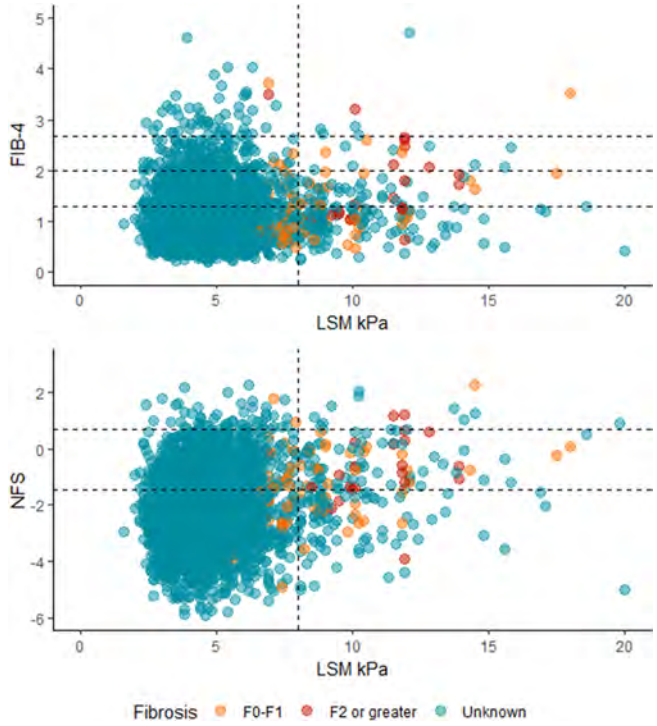

Figure 1. Scatterplots of LSM using TE and FIB_4 and NFS.

Conclusions: A significant fraction of patients with FIB4 or NFS values suggesting the absence of advanced fibrosis have elevated LSM above the 8 kPa cutoff. This raises the question regarding the utility of FIB-4 and NFS as the first step in the screening for liver fibrosis in the general population.

FRI031

Utilizing pre-existing imaging and data lake technology in the search of clinically neglected non-alcoholic fatty liver disease (NAFLD)

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is a major cause of liver morbidity and an independent risk for cardiovascular events, type 2 diabetes and mortality. However, it is rarely diagnosed when reported as an incidental observation when abdominal diagnostic imaging is performed for other clinical purposes. The aim of our study was to identify patients with clinically unrecognized fatty liver disease – and the proportion of it associated with insulin resistance and/or diabetes - in the Helsinki University hospital district utilizing data lake technology to mine the electronic health care records.
Method: We used a phrase recognition script to analyse all radiological reports for patients with any abdominal imaging (US, CT, MRI) performed during the last 6-year period in the Helsinki University Hospital electronic data lake, which contains radiology reports, laboratory data and ICD codes for a catchment area of 1.6 million people. We analysed all available glucose laboratory data for the patients with fatty liver disease (FLD) on imaging or with the ICD-10 code K76.0 to identify patients with diabetes: fasting plasma glucose >7, random glucose >11.1 or 2 h glucose during OGTT >11.1 mmol/l. or HbA1c >48 mmol/mol. The script utilised word stems and phrases indicative for FLD or excluding it (e.g."echog* liver," "fatty liver," etc). For validation, a set of 1000 randomly sampled radiological reports were manually read and a subspecialist in abdominal radiology reanalysed the original imaging studies constituting 10% of the validation set (33 US, 33 MRIs and 33 CTs).
Results: A traditional search found 360 patients with the ICD-10 code K76.0 while the phrase recognition script recognized 23 425 patients with radiologically reported FLD. In the validation, only 16/1000 radiology reports were found to be false positive in the script recognition and 2/99 imaging studies were found to be false positive in reanalysis of the images. Altogether, 4425 (19%) patients with fatty liver on imaging had diabetic glucose and/or HbA1c values.
Conclusion: Radiological FLD is a clinically neglected condition. Even when FLD is suspected the clinical diagnosis is not recorded in 98% of cases. Only 19% of the subjects found to have FLD had diabetic laboratory values suggesting associated co-morbidity, but the true prevalence of diabetes is unknown. Data lake technology and phrase recognition data mining provide a tool to discover undiagnosed NAFLD patients.

FRI032

Factors associated with NAFLD and advanced liver fibrosis and accuracy of liver biopsy in patients with diabetes mellitus type 2: a cross sectional study

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Background and Aims: NAFLD is commonly found in obese patients and with conditions that may be related to obesity, such as insulin resistance, dyslipidemia, hypertension and type 2 diabetes (T2DM). The prevalence of NAFLD in T2DM patients is high and the two conditions often coexist. The aim of our study was to assess the prevalence and to estimate the risk factors of NAFLD and liver fibrosis (LF) in patients with T2DM, as well as to explore accuracy of liver biopsy.
Method: This is a cross-sectional study of adult patients with T2DM. All patients had transient elastography (TE) after overnight fasting using Fibroscan®. Patients were considered to have hepatic steatosis as CAP ≥ 238 dB/m. LF was considered as LSM >7 kPa and advanced fibrosis (ALF) as LSM ≥ 9.6 kPa or ≥ 9.3 kPa according to the M or XL probe, respectively. Suitable patients underwent a percutaneous liver biopsy. ALF was defined as biopsy fibrosis stage ≥ F3.
Results: A total of 679 patients were included in this cross-sectional study, mean age 65.2 ± 11.6, 54.3% (n = 369) males, BMI 30.75 ± 5.15 kg/m^2 and prevalence of obesity and central obesity was 52.5% (n = 357) and 73.9% (n = 502), respectively. The prevalence of NAFLD was 83.6% (n = 568). Independent factors associated with NAFLD were higher BMI, longer T2DM duration, higher serum triglyceride, lower levels of vitamin D, higher CRP and higher HOMA-IR. The prevalence of LF was 27% (n = 183) and ALF 13% (n = 86). On multivariate analysis independent factors associated with ALF were female gender, higher BMI, higher levels of ALT, GGT and CRP, and lower levels of cholesterol. Liver biopsy was performed in 105 patients. F3-4 disease was detected in 38 (36.1%). The sensitivity, specificity, PPV and NPV of increased LSM to detect histological F3-4 disease were 41.03% (95%CI 25.6–57.9), 74.24% (95%CI 62–84.2), 48.5%

(95%CI 35–62.1), and 68% (95%CI 61.3–74.1), respectively, with AUC of 0.58. Sixty-six patients were misclassified (62.85%).
Conclusion: In patients with T2DM there is high proportion of NAFLD, liver fibrosis and advanced liver fibrosis according to TE. Risk factors can help in early identification of NAFLD, LF and ALF. TE is practical and convenient, and can help in identifying patients in which the liver biopsy would be beneficial. However, there, low accuracy in T2DM patients could be disadvantage. This study points out the complexity disease-specific factors and impact of T2DM on the risk factors and TE accuracy.

FRI033

FIB-4 first strategy for non-alcoholic fatty liver disease might not be appropriate for ruling-out advanced liver fibrosis with current cut-off values in patients with type 2 diabetes mellitus

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Background and Aims: There are proposals to implement "FIB-4 First" strategy to triage patients entering a Non-alcoholic fatty liver disease (NAFLD) assessment pathway with FIB-4 threshold of 1.3 as acceptable for reliably ruling-out advanced liver fibrosis. We intended to test this strategy in patients with type 2 diabetes mellitus (T2DM), known of having increased risk of liver fibrosis.
Methods: Retrospective analysis of prospectively enrolled cohort of patients with T2DM at diabetes clinic who all underwent liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) by transient elastography (TE) in addition to standardized laboratory work-up sufficient to calculate FIB-4 score. We used LSM cut-off value of 7.9 kPa to rule-out and 9.6 kPa to rule-in advanced fibrosis respectively. Patients were followed until death or censored date.
Results: A total of 454 DM patients (236; 52% males) with mean age (SD) of 62.5 (12) years were recruited. In patients with FIB-4 <1.3 (N = 268) there were 45 (16.8%) patients with LSM>7.9 (of them 21 (7.8%) had LSM>9.6 kPa indicative of advanced fibrosis/cirrhosis). During the median follow up time of 25 months (interquartile range: 9–39), a total of 106 (23.3%) patients experienced an adverse event: cardiovascular in 50 (11%) patients, infection-related in 31 (6.8%), diabetes-related in 22 (4.8%), oncological in 16 (3.5%), whereas there were no liver-related complications. Seventeen (3.7%) patients died during the follow up (all deaths non-related to liver disease). In Cox regression analysis only age (OR = 1.05; 95%CI = 1.027–1.073; p < 0.001) and with borderline significance HbA1c levels (OR = 1.008; 95%CI = 1.000–1.017; p = 0.059) were significant predictors of any morbidity or mortality at follow-up, but not gender, smoking, statin use, BMI, FIB-4, LSM nor CAP.
Conclusion: FIB-4 threshold of 1.3 in T2DM population might not be appropriate for ruling-out advanced liver fibrosis, although in short term it doesn't pose particular clinical issue since most of the complications in 2-year period are related to DM and not to liver. This conclusion is hampered by the lack of liver biopsy to confirm noninvasive results obtained in this study.

FRI034

Accuracy of cytokeratin-18 (M30 and M65) in detecting non-alcoholic steatohepatitis and fibrosis: a systematic review and meta-analysis

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Background and Aims: The association between elevated cytokeratin 18 (CK-18) levels and cell death in the liver has made circulating CK-18 a candidate biomarker to differentiate non-alcoholic fatty liver (NAFL) from non-alcoholic steatohepatitis (NASH). However, there is high variability among study results. We aimed to provide summary estimates with increased precision on the accuracy of CK-18 antigens (M30, M65) for detecting NASH, fibrotic NASH and fibrosis among NAFLD adults.
Method: We searched five electronic databases to retrieve studies evaluating CK-18 against a liver biopsy as the reference standard in NAFLD adults. Reference screening, data extraction and quality assessment (QUADAS-2) were independently conducted by two authors. Reported sensitivities, specificities, sample size and prevalence were utilized to construct 2 × 2 tables. Meta-analyses were performed for five groups based on the CK-18 antigens and target conditions, using one of two methods, based on availability of data: a linear mixed-effects multiple thresholds model and a bivariate logitnormal random-effects model.
Results: A wide range of disease prevalence was observed (Table 1). Most studies (86%; 32/37) had included patients with mean BMI <35. No study reported a pre-defined cut-off value. Twenty-nine out of 37 studies provided sufficient data for inclusion in any of the meta-analyses. The highest summary area under the receiver operating characteristic curve (AUC) was observed for M65 in diagnosing NASH (0.82; 95% CI: 0.69–0.91), all others had AUC <0.80. Thirteen studies used CK-18 as an ingredient of a biomarker panel, with higher reported AUC for these panels.

Table: Summary of meta-analysis results.

Target condition	CK-18 antigen	No of studies	No of patients	Prevalence of target condition, % mean (range)	AUC (95% CI)	No of unique cut-offs	Range of cut-off values (U/L)
NASH	M30	21	3,403	57 (21–85)	0.74 (0.67–0.81)	40	111–670
NASH	M65	6	414	53 (32–75)	0.82 (0.69–0.91)	11	340–1183
Fibrotic NASH	M30	3	1,271	27 (21–62)	0.73 (0.57–0.85)	7	113–464
Significant fibrosis	M30	5	1,155	48 (18–59)	0.68	5	122–285
Advanced fibrosis	M30	5	1,513	21 (19–36)	0.75	5	216–396

Conclusion: Our results show limited ability for CK-18 as a stand-alone test for identifying NASH and fibrosis staging. The M65 antigen and biomarker panels including CK-18 showed improved performance, but further external validation studies are needed to obtain credible estimates of the diagnostic accuracy of these panels.

FRI036

Composite biomarkers selected by machine learning predict severe fibrosis in NASH

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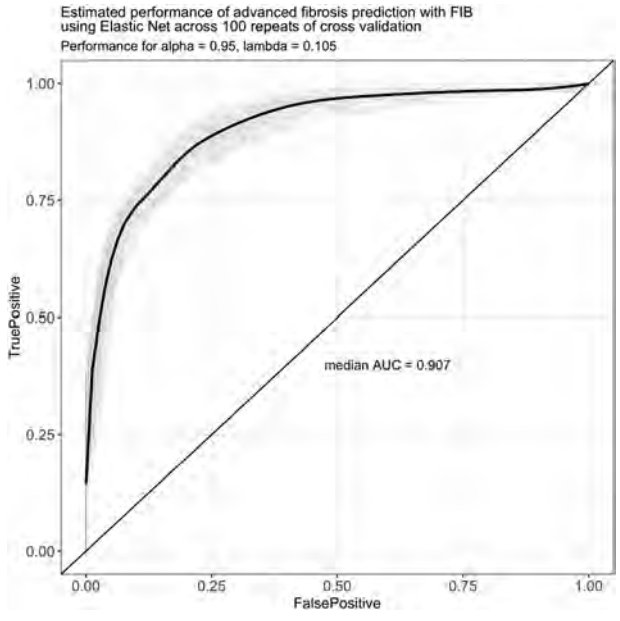
Background and Aims: Distinguishing patients with more advanced stages of liver fibrosis in non-alcoholic steatohepatitis (NASH) is critical for patient stratification, treatment, and prognosis. However, published models based on circulating biomarkers lack discriminatory power and replicability across cohorts; thus current diagnosis of fibrotic stage still requires invasive liver biopsies. Here we employ a machine learning technique called Elastic Nets with cross-validation to train and test novel composite serum biomarker models in a cohort of 420 patients from the Harvard Fibrosis Network (HFN) to distinguish advanced stages of NASH.
Method: Sera from 420 biopsy-proven NASH (F0-F4) and non-alcoholic fatty liver (NAFL) patients were analyzed. With samples randomized into 6 × 96-well plates we conducted 2 multiplexed ELISA assays of 58 fibrotic (FIB) and 76 immune-related (IMM) biomarkers apiece, using the Luminex platform. We used the glmnet package in R to conduct the Elastic Net algorithm with cross-validation to reduce the number of biomarkers and clinical features, and obtain models to predict significant (F2-F4), advanced (F3-F4), and F4 fibrotic stages of NASH (resulting in 6 models total). We also applied repeated loops of cross-validation to predict out-of-sample performance of our selected models by area under the curve (AUC) of the receiver operating characteristic (ROC).
Results: The best performing model is able to predict NASH with advanced fibrosis in our sample using 9 biomarkers and patient age with cross-validated median AUC = 0.907 predicted for performance in an independent cohort. Our other models could predict significant fibrosis (NASH F2-F4) and NASH F4 using combinations of just 3–11 biomarkers, patient BMI, and age, all with cross-validated predicted performance of AUC >0.85. Our models consist of common subsets of biomarkers, both novel and previously reported. The predicted out-of-sample performance of these models exceeds that of standard clinical models in this cohort (AUCs for BARD = 0.7, NAFLD score = 0.76, FIB-4 = 0.84 compared to cross-validated AUC = 0.91).



Conclusion: In a large cohort of NASH and NAFLD patients, we successfully used machine learning to develop predictive models to classify the severity of fibrosis in NASH. These outperform standard non-invasive clinical models. Importantly, we identified composite biomarker panels that can distinguish NASH F4 from NASH F3, an unmet need in clinical diagnostics. These cross-validated models should be further validated in independent cohorts.

FRI037

Low transient elastography score appropriately identifies patients that can stay within primary care practice

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Background and Aim: Non-alcoholic fatty liver disease (NAFLD) is the most common liver disorder in western countries. Transient Elastography (TE) is a convenient, non-invasive test to screen NAFLD patients for fibrosis thereby selecting patients who need evaluation for progressive disease and complications of portal hypertension. Given the high prevalence of NAFLD, referral of all patients to specialist care is not feasible. Therefore, we created an open access TE referral system with primary care providers (PCPs) to stratify based on TE score. Aim: To determine referral trends for low risk patients using open access TE.

Characteristics of study population (n = 212)			
	Not referred to hepatology (n = 160)	Referred to hepatology (n = 52)	p value
Age (years)	**54.3 (12.1)**	**50.2 (14.3)**	**0.04**
Sex (% female)	69 (43.1)	19 (36.5)	0.5
Race (%)			0.43
Caucasian	100 (65.4)	31 (60.8)	
Hispanic	24 (15.7)	9 (17.6)	
African-American	12 (7.8)	8 (15.7)	
Asian	16 (10.5)	3 (5.9)	
Other	1 (0.7)	0 (0)	
BMI (kg/m^2)	31.3 (6.8)	32.7 (7.4)	0.23
ALT (IU/L)	**43 (30.8)**	**73.4 (67.7)**	**<0.001**
DM2 (%)	34 (23.8)	11 (21.2)	0.85
PLT (K/uL)	248.1 (71.1)	261.2 (66.1)	0.29
A1C (%)	6.5 (4.6)	6.1 (1)	0.55
Alcohol abuse (%)	15 (10.9)	8 (15.7)	0.52
Fibroscan score (kPa)	**5.0 (1.1)**	**5.4 (1)**	**0.03**
CAP score (dB/m)	296.99 (53.3)	294.22 (61.1)	0.76
FIB-4	1.23 (1.1)	1.24 (1.2)	0.97
NFS	-2.31 (4.1)	-2.27 (1.5)	0.96
FIB-4 ≥ 2.67 (%)	6 (5.2)	2 (4.7)	1
NFS ≥ 0.676 (%)	7 (13)	1 (3.2)	0.27
CAP score ≥ 280	68 (81)	30 (85.7)	0.72
Steatosis on ultrasound (%)	68 (81)	30 (85.7)	0.72
Splenomegaly (%)	8 (9.6)	4 (11.4)	1
Portal hypertension (%)	4 (6.2)	4 (14.8)	0.35

Methods: In August 2017, an open access program was established whereby PCPs order TE for fibrosis assessment on NAFLD patients. A TE score < 7 kilopascals (kPa) was considered low-risk and would recommend management by the PCP. TE scores ≥ 7 kPa were considered high-risk and prompted a hepatology evaluation. Data were collected on each referral including demographics, practice type of the ordering physician, TE score, CAP score, serological testing, comorbidities, imaging and patient follow up with hepatology.
Results: Seventy percent (212/303) of those initially referred using the open access TE system had a score of <7 kPa. Despite this score, 25% (52/212) of these patients were still referred and evaluated by hepatology. Those were referred for evaluation tended to have a higher TE score (5.4 kPa vs 5.0 kPa, p = 0.03), ALT values (73.4 IU/L vs 43 IU/L, p < 0.001) and were slightly younger (50.2 y/o vs 54.3 y/o, p = 0.04). There was no statistically significant difference in race, BMI, A1c, FIB-4 score, NFS score, CAP score, or findings of steatosis and portal hypertension on imaging between the group eventually seen by hepatology and those referred back to PCP.

Conclusion: Use of screening TE in the primary care setting is a useful tool to risk stratify NAFLD patients, allowing efficient utilization of healthcare resources by referring low risk patients back to the PCP for lifestyle modifications. Patients with TE score <7 kPa had concordantly low FIB-4 and NFS scores demonstrating that our open access TE program and referral algorithm was able to appropriate risk stratify patients. Still, higher ALT values tend to trigger appropriate hepatology evaluations in this group. Linkage to care remains an important part of this process and clear communication between primary care and hepatologists is paramount.

FRI038

Phenome-wide association study of the FIB-4 index in a large, populational-based study in the United States

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Background: The fibrosis-4 index (FIB-4) is a noninvasive test that has been validated in patients with nonalcoholic fatty liver disease (NAFLD), but is increasingly utilized to identify at-risk patients in the general population. We report a large-scale analysis of associations between FIB-4 and diagnostic phenotypes (PheCodes) in a general electronic health record (EHR).
Method: Using the EHR database of the Renown Health system in Reno, Nevada, 57,764 individuals aged 40–65 years were identified with any high or always low FIB-4 scores, based on standardized lab values across the last four years. After application of stringent exclusion criteria for hepatic comorbidities unrelated to NAFLD such as alcohol and drug abuse and viral hepatitis, 41,326 individuals remained eligible (the curated cohort). ICD9/10 codes were extracted and mapped to 1,757 PheCodes. On average, an individual had 17 PheCodes assigned. Linear regression was used to evaluate associations between the incidence of each phenotype group containing at least 250 participants, adjusted for age and gender, using a modification of the PheWAS program in R. A standard correction for the false discovery rate was performed, and all adjusted p-values less than 10^{-5} were considered for statistically significant associations.
Results: In the non-curated cohort, FIB-4 scores were significantly associated with numerous expected phenotypes with large effect size (>8) including chronic liver and hematologic conditions ($p < 10^{-320}$). In total, 366 phenotype codes ($p < 10^{-5}$) were identified. In contrast, the curated cohort generated fewer significant PheCodes associated with FIB-4 (98 codes, $p < 10^{-5}$) and a much lower effect sizes (mean effect size, 0.45 vs 1.92 in the non-curated cohort). These notable differences in significant associations and effect sizes between the non-curated and curated cohorts suggest that the predictive value of FIB-4 decreases drastically when eliminating hepatic comorbidities unrelated to NAFLD. In the curated cohort, the phenotypes significantly associated with FIB-4 with the largest effect sizes (all < 1) were related to cardiac and respiratory disorders.
Conclusion: These findings from a large general population EHR database suggest that elevated FIB-4 scores are often strongly associated with a variety of phenotypes unrelated to NAFLD even after application of exclusion criteria. Thus, careful cohort selection is necessary when utilizing FIB-4 in such populations to assess the epidemiology and outcomes of NAFLD.

FRI039

A combined and sequential non-invasive approach to diagnosing non-alcoholic steatohepatitis in patients with non-alcoholic fatty liver disease and persistently normal alanine aminotransferase levels

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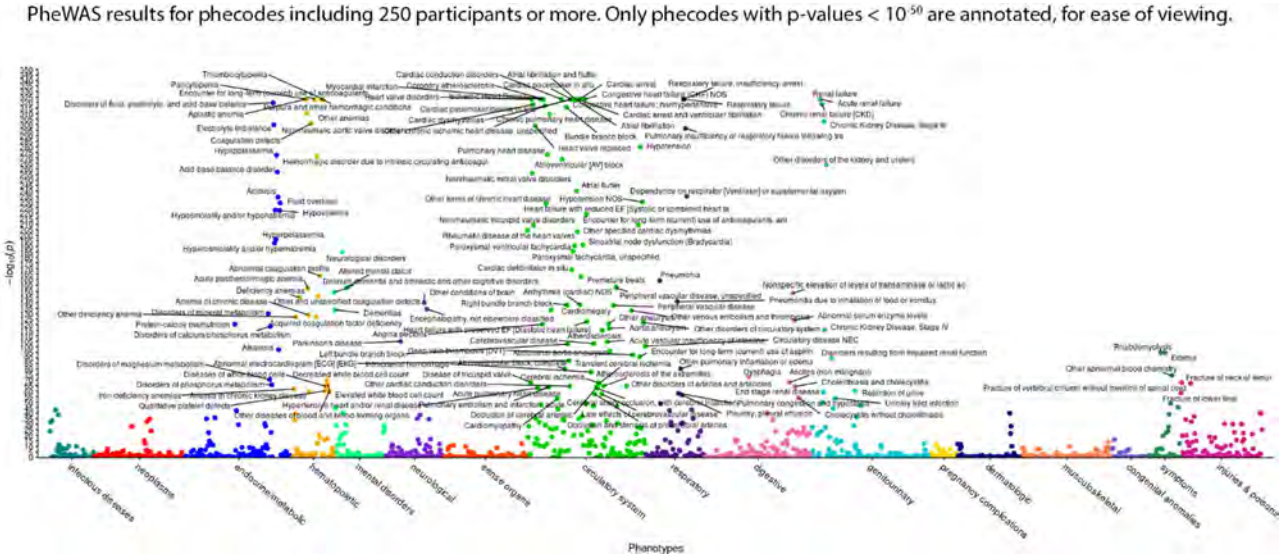

Figure: (abstract: FRI038)

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Background & Aim: Liver disease severity is often not investigated further in patients with imaging-confirmed non-alcoholic fatty liver disease (NAFLD), who have normal alanine aminotransferase (nALT) levels. Early diagnosis of non-alcoholic steatohepatitis (NASH) is needed for preventing further progression in NAFLD patients. We aim to test whether serum Golgi protein 73 (GP73) levels predicts NASH in patients with biopsy-confirmed NAFLD and nALT levels, and develop a non-invasive model to diagnose NASH in this group of patients.

Methods: Serum GP73 and cytokeratin 18 M30 fragments (CK18-M30) levels were measured in 345 patients with biopsy-proven NAFLD. We have developed a new G-NASH model (that included serum GP73 concentration) and combined it with serum CK18-M30 measurement in a sequential non-invasive approach to accurately identify NASH among patients with NAFLD and persistently nALT levels.

Results: 105 (30.4%) patients had persistently nALT, 53 (50.5%) of which had histologically-confirmed NASH. Both serum GP73 and CK18-M30 levels alone had poor diagnostic accuracy for identifying NASH (55.2% and 51.6% respectively) in patients with NAFLD and persistently nALT. In contrast, the newly developed G-NASH model

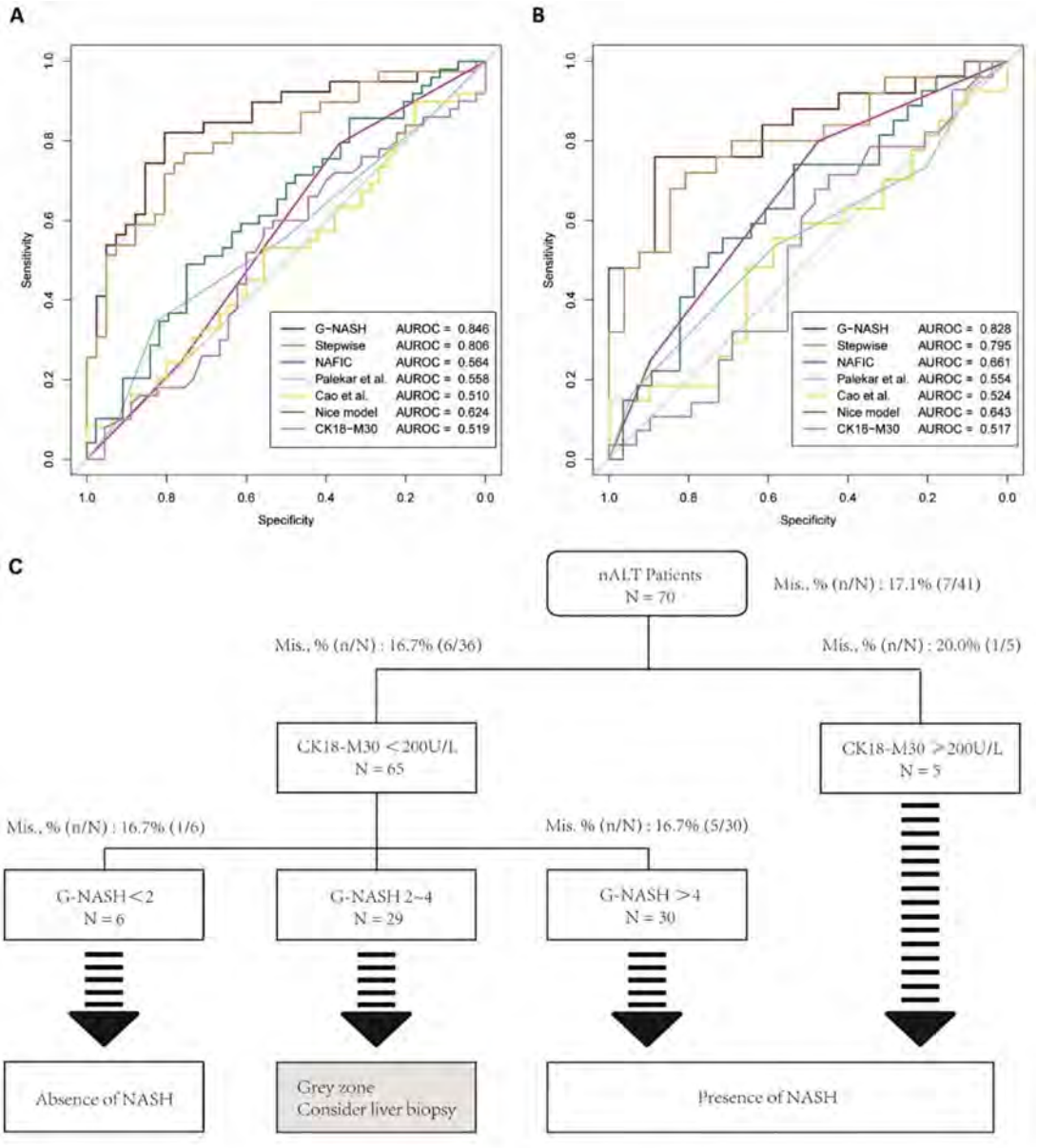

Figure 1. A&B. Receiver operating characteristic curves of various non-invasive clinical scoring systems for the prediction of NASH among NAFLD patients with persistently nALT. C. Combined and sequential non-invasive approach to predict NASH among NAFLD patients with persistently nALT levels by using serum CK18-M30 levels and the G-NASH model.

(A) using a cut-off of serum ALT levels <40 U/L for both sexes. (B) using a lower cut-off of serum ALT ≤35 U/L in men (n = 48) and ≤23 U/L in women (n = 16). (C) Mis.: misdiagnosis.

Figure: (abstract: FRI039)

performed best when compared to other established non-invasive scoring systems (area under the receiver operator characteristic curve [AUROC] 0.846, 95% confidence intervals 0.757 to 0.934). Moreover, by using our proposed combined and sequential non-invasive approach, 82.9% (34 out of 41) of patients with NASH were correctly identified.

Conclusions: NASH is highly prevalent in NAFLD patients with persistently nALT levels. The G-NASH model can accurately identify NASH in this patient group.

FRI040

Macrophage markers do not add to the prediction of liver fibrosis by transient elastography in patients with non-alcoholic fatty liver disease

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Background and Aims: Fibrosis staging by non-invasive tests is essential in non-alcoholic fatty liver disease (NAFLD). Measurement of liver stiffness by transient elastography (TE) is a well-established method for liver fibrosis assessment in NAFLD. We have previously shown that macrophage marker sCD163 is an independent predictor for fibrosis in NAFLD, and that combining sCD163 with e.g. NAFLD Fibrosis score improves the precision. In the present study we tested whether the combination of macrophage markers and TE improves fibrosis prediction compared to the individual parameters.

Method: We measured macrophage markers soluble CD163 (sCD163) and mannose receptor (sMR) using in-house ELISA assays in two independent cohorts from Italy (n = 141) and Sweden (n = 70) with biopsy-proven NAFLD and available TE.

Results: In the Italian cohort, TE and sCD163 showed similar moderate associations with liver fibrosis (rho = 0.56, p < 001 and rho = 0.45, p < 0.001, respectively). TE had an area under the Receiver Operating Characteristics curve (AUROC) (with 95% CI) for F2 fibrosis: 0.79 (0.72–0.87), F3: 0.81 (0.73–0.89), F4: 0.95 (0.90–1.0). sCD163 also predicted fibrosis well [F2: 0.71 (0.63–0.80), F3: 0.82 (0.74–0.90), F4: 0.89 (0.76–1.0)]. However, combining sCD163 and TE did not improve the AUROCs significantly [F2: 0.79 (0.72–0.87), F3: 0.85 (0.78–0.92), F4: 0.97 (0.93–1.0)]. In the Swedish cohort, TE showed a closer association with fibrosis (rho = 0.73, p < 0.001) than sCD163 (rho = 0.42, p < 0.001) and sMR (rho = 0.39, p < 0.001). TE predicted fibrosis well [F2: 0.88 (0.80–0.97), F3: 0.90 (0.83–0.97), F4: 0.87 (0.78–0.96)], whereas sCD163 did not (best AUROC 0.75). sMR showed a better prediction [F2: 0.68 (0.56–0.81), F3: 0.82 (0.71–0.92), F4: 0.79 (0.66–0.93)], but the addition of sMR did not further improve the prediction of fibrosis by TE.

Conclusion: In these cohorts of NAFLD patients, TE was superior to macrophage markers for fibrosis prediction and in contrast to our hypothesis the addition of these markers to TE did not improve its predictive capability.

FRI041

Diagnostic accuracy of controlled attenuation parameter compared to ultrasound for detecting steatosis in children with obesity

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Background and Aims: Current screening tools, alanine amino-transferase (ALT) and ultrasound (US), have insufficient accuracy for detecting Non-alcoholic Fatty Liver Disease (NAFLD) in children with obesity. The aim of this study is to determine the diagnostic accuracy of Controlled Attenuation Parameter (CAP) in detecting and grading steatosis in a screening setting and perform a head-to-head comparison with US.

Method: Sixty children (57% male) with severe obesity (median BMI z-score 3.37; median age 13.7 years) were evaluated. All underwent CAP measurement and US using a standardized 4-item scoring system. Magnetic Resonance Spectroscopy Proton Density Fat Fraction (MRS-PDFF) was used as reference standard. ROC curve analyses were performed to determine diagnostic performance and optimal screening cutoffs.

Results: Steatosis was present in 36/60 (60%) children. The areas under the ROC (AUROC) of CAP for the detection of grade ≥ S1, ≥ S2 and ≥ S3 steatosis were 0.79 (95% CI:0.67–0.89), 0.75 (95% CI:0.62–0.85) and 0.79 (95% CI:0.67–0.89), respectively. The AUROC of US for the detection of grade ≥ S1 steatosis was 0.68 (95% CI:0.55–0.80) and was not significantly different from CAP (p = 0.11). For detecting ≥S1 steatosis, CAP had a sensitivity of 75% and a specificity of 75% at its optimal cutoff of 277 dB/m. US had a sensitivity of 61% and a specificity of 71% for detecting ≥ S1 steatosis at its optimal cutoff (US steatosis score ≥ 2). When using echogenicity of liver parenchyma as only scoring item, US had a sensitivity of 70% and specificity of 54% to detect ≥S1 steatosis. The difference in specificity of CAP and US

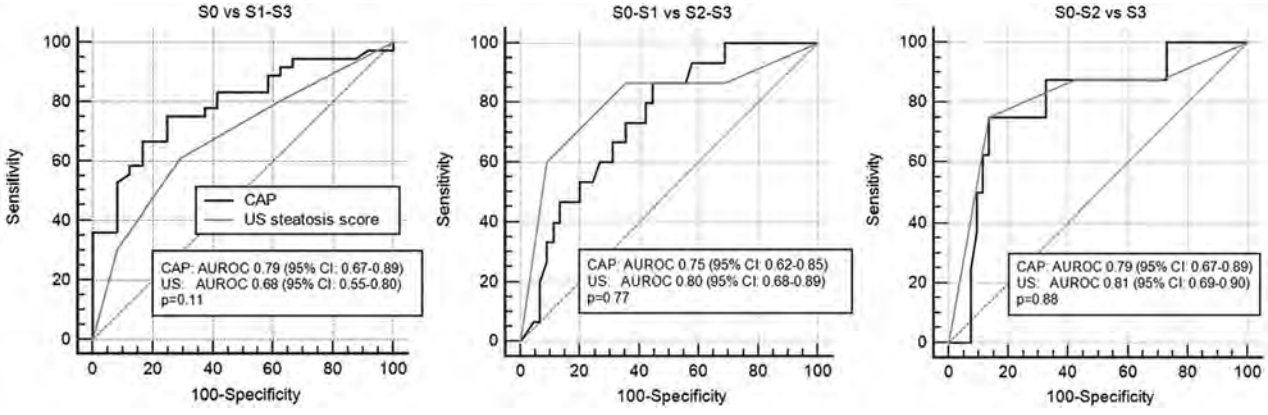

Figure: (abstract: FRI041)

when using only echogenicity of liver parenchyma of 21% was significant (p = 0.04).
Conclusion: The overall performance of CAP is not significantly better than US in detecting steatosis in children with obesity, provided that standardized scoring of US features is applied. When US is based on liver echogenicity only, CAP outperforms US in screening for any steatosis (≥S1).

FRI042
ELF test should be used concurrently with elastography in NAFLD to maximize diagnostic accuracy
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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is the leading cause for secondary care referrals in most western countries. Despite its high prevalence, only a minority of patients develops fibrosis and subsequent liver-related outcomes. The ELF test is a validated tool for non-invasive assessment of liver fibrosis and is recommended by the National Institute for Clinical Excellence (NICE) in the UK for screening NAFLD patients for advanced fibrosis. We explored the concordance of ELF with FibroScan® and its diagnostic accuracy compared to liver biopsy in consecutive patients referred because of a high ELF score.
Method: We selected all patients referred from 2014 to 2019 according to local referral pathways because of a suspicion of NAFLD and an ELF test ≥9.5. Clinical and laboratory data were collected. ELF test was compared to liver biopsy and/or liver stiffness assessed with FibroScan®.
Results: 292 patients fulfilled our inclusion criteria. Characteristics of the population were: 50% male, mean age 64 ± 10 years, mean BMI 32 ± 6 Kg/m^2, 47% had diabetes, 66% dyslipidaemia, 68% hypertension. Liver biopsy was available for 80 (27%) patients and FibroScan® measurements for 233 (80%) patients. 24 (30%) liver biopsies showed advanced fibrosis and 57 (71%) showed NASH. Liver stiffness values were ≥ 8 kPa in 69 (30%) patients and ≥ 10 kPa in 45 (19%). Therefore, the concordance of FibroScan® and ELF for advanced fibrosis (cut-off 10 kPa) was 19% and there was a significant discordance (FibroScan® <6 kPa) in 105 (45%) of the cases. Forty-eight (60%) patients with a high ELF score had no or minimal fibrosis (F0-F1) on liver biopsy; only eight and four of these patients had FibroScan® values above 8 kPa and 10 kPa respectively. All patients with biopsy proven advanced fibrosis had FibroScan® values >8 kPa. We could not identify independent predictors of advanced fibrosis in our cohort.
Conclusion: The ELF test has a poor concordance with liver stiffness for the diagnosis of advanced fibrosis. When ELF is used as a screening tool, the use of a confirmatory second non-invasive test is warranted for positive results, in order to better stratify patients needing a liver biopsy.

FRI043
Evaluation of a novel histology-based fibrosis phenotypic composite score and its correlation with NASH-CRN fibrosis scores in patients with NASH
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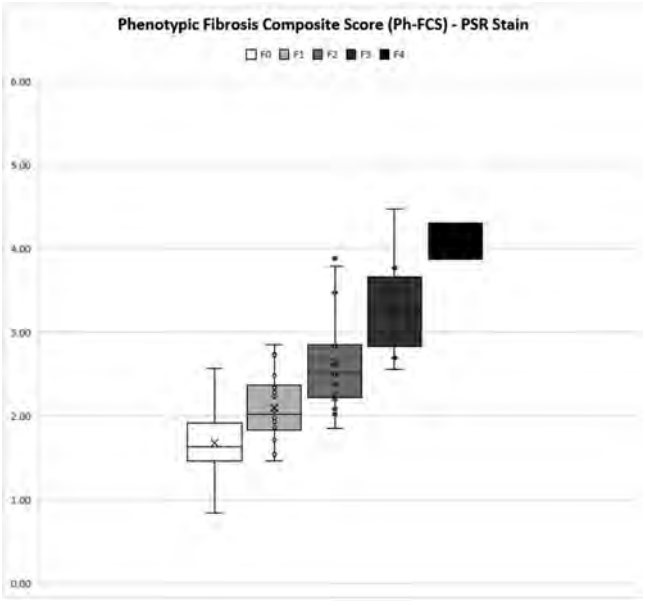
Background and Aims: We have previously shown that the Phenotypic Fibrosis Composite Score (Ph-FCS) calculated by the FibroNest image analysis platform from second harmonic generation (SHG) images correlates with the NASH-CRN fibrosis scores. Ph-FCS is a novel continuous phenotypic scoring and quantifier of fibrosis. In this study, the same slides imaged non-destructively by SHG have been stained, digitized and then quantified with FibroNest. This study evaluates the performance of the Ph-FCS obtained from stained slides and its relationship with NASH-CRN fibrosis scores.
Method: This retrospective study comprised a cohort of 77 patients with NASH diagnosed by histologic assessment of liver biopsy according to NASH CRN criteria by pathologists (F0(21), F1(17), F2 (20), F3(15), F4(4)). FFPE sections (3–4 microns) of biopsies were stained with picro sirius red (PSR, Abcam Kit ab150681) and imaged at 20X in white light with an Aperio AT2 Digital Pathology system. Using FibroNest© for image analysis, the fibrosis phenotype is described for its collagen content and structure (12 traits), the morphometric traits of the collagen fibers (12), and fibrosis texture traits (7). Each morphometric and texture trait is quantified with 7 parameters (qFPs) to account for severity, progression, distortion and variance for both fine and assembled collagens, resulting in a total of 315 qFPs. Meaningful qFPs are combined to calculate the normalized Ph-CFS. The sensitivity of the Ph-CFS to the PSR process is also evaluated on a separate group of 5 biopsies (thickness: 2–5 micron; bath time: 10–60 min).
Results: The Ph-CFS correlates with fibrosis stages (p < 0.00001) and differentiates between fibrosis F1 to F4 stages. In the development of the score, non-adequate biopsies (<10 mm long) limited the performance of the computerized method and were removed from the final analysis. In order to obtain a Ph-FCS of similar performance as the one obtained using SHG, we doubled the amount of meaningful qFPs (from 30 to 70) to generate a higher image analysis signal to noise capable to offset any loss in collagen detection (vs SHG). The Ph-FSC appears to be very robust as it varies less than 5% when the thickness of the section varies within 1 micron and the staining bath time varies within 10 mins.



Conclusion: The Ph-CFS calculated with FibroNest© from histopathology stained sections is a valuable and reliable evaluation of fibrosis severity and progression in patients with NASH.

FRI044

Serum exosomal miRNA-4668-5p as potential biomarker for advanced fibrosis in non-alcoholic fatty liver disease

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Background and Aims: Nonalcoholic fatty liver disease (NAFLD) is becoming leading cause of chronic liver disease. As fibrosis is the main prognostic factor in patients with NAFLD, it is important to identify advanced fibrosis. In this study, we analyzed serum exosomal miRNA and tissue miRNA from biopsy-proven NAFLD patients and identified the role of miRNA in progression of fibrosis.
Method: Sera and tissue were collected from 41 patients with biopsy-proven NAFLD without other chronic liver disease between November 2016 and January 2018. Sera were stored at −80°C and thawed for isolation of the exosome. Exosomes were isolated from sera using an exosome isolation kit. Total RNA was extracted from exosomes and microarray was performed. Liver tissues were stored at −80°C and subjected to real-time PCR. Overexpression and inhibition of miRNA were achieved by transfection of miRNA mimic and miRNA inhibitor in hepatic stellate cell line (LX-2), respectively.
Results: Mean age and BMI were 53.5 ± 12.3 years and 29.9 ± 4.6 kg/m^2, respectively. Female was dominant (n = 34, 82.9%). In microarray analysis, total 2,578 miRNAs were identified. We classified patients into non-advanced fibrosis group (F0-2, n = 25) and advanced fibrosis group (F3-4, n = 16). 40 miRNAs expression were significantly increased in advanced fibrosis group comparing with non-advanced fibrosis group. Among them, miRNA4668 were increased more than 8 times in advanced fibrosis group comparing with non-advanced fibrosis group. In tissue, the expression of miRNA 4668-5p (miR-4668-5p) were significantly decreased in advanced fibrosis group comparing with non-advanced fibrosis group. Overexpression of miR-4668-5p increased expression of profibrotic genes (TGF-β1, collagenase 1a1, and α-SMA) in LX-2, whereas inhibition of miR-4668–5p decreased expression of profibrotic genes in LX-2. (Figure).

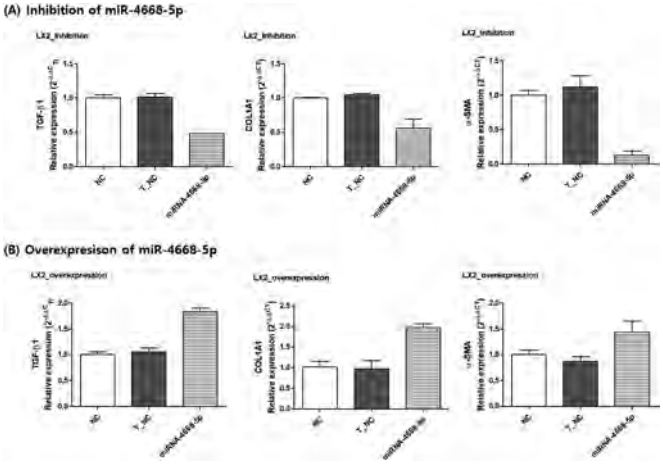

Figure: Profibrotic gene expression in LX-2 after inhibition of miR4668-5p (A) and overexpression of miR-4668-5p (B).

Conclusion: miR-4668-5p expression was significantly increased in exosome from patients with advanced fibrosis compared to non-advanced fibrosis group. miR4668-5p could be useful biomarker and might be therapeutic target for advanced fibrosis in NAFLD.

FRI046

Patient-reported symptoms and impact in non-alcoholic steatohepatitis: an evaluation of the NASH-check, a novel prom in NASH

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Background and Aims: NASH-CHECK is a newly developed patient-reported outcome measure (PROM) assessing symptoms and health-related quality of life (HRQOL) in nonalcoholic steatohepatitis (NASH). The aim of the study was to conduct an evaluation of the preliminary dimensional structure of this PROM. The evaluation was guided by a conceptual model prepared during the initial development of NASH-CHECK, from which items were categorised into logical groupings comprising 10 symptoms items and 21 HRQOL items (activity limitations = 8 items; emotions and lifestyle issues = 13 items).
Method: Data from a randomised, double-blind, placebo-controlled phase 2 trial of tropifexor in adult patients with NASH were used for the evaluation. Analyses included item correlations, exploratory factor analysis and Rasch analysis.
Results: The analysis sample included 104 patients with NASH fibrosis grades 1 to 3 (54.8% female; mean [standard deviation] age = 51.2 [12.7] years; mean [standard deviation] body mass index = 32.5 [6.1]). Type 2 diabetes was present for 60 (65.4%) patients. Figure 1 shows a summary of the preliminary structure of NASH-CHECK resulting from the analyses. The results supported a 4-item cognitive symptoms subscale with the remaining symptoms items (e.g. pain, bloating, fatigue, itch) as individual items. For HRQOL, analysis supported the distinction between activity limitations and emotions & lifestyle. Analysis supported an overall activity limitations summary score which can be further divided into two activity limitations subscales (daily activities; ambulation). For emotions & lifestyle, production of an overall psychosocial summary was supported along with two subscales (emotions and social). Some items were highly correlated with each other (>0.80) suggesting potential content overlap (e.g. single symptoms items fatigue and need to rest, ambulatory items within the activity limitations subscales). In addition, one item (food restriction) showed a lack of association with other HRQOL items.

Figure: Preliminary dimensional structure of NASH-CHECK.

Conclusion: The results provide evidence for a preliminary dimensional structure for NASH-CHECK that is in line with the proposed logical groupings in the conceptual model. Further analyses using new trial data are planned to confirm the dimensional structure of NASH-CHECK.

FRI047

The FGF19 analogue aldafermin improves non-invasive tests in patients with non-alcoholic steatohepatitis

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Background and Aims: Nonalcoholic steatohepatitis (NASH) represents an epidemic health crisis with broad impact on public health. Developing therapeutics for NASH poses a vexing challenge, which requires invasive procedures such as liver biopsy. Several inexpensive, simple, commonly used non-invasive tests (NITs), such as AST to platelet ratio index (APRI) and FIB-4 index, can predict liver-related outcomes and have been used to identify high-risk NASH patients from primary care settings. Aldafermin (previously known as NGM282), a non-tumorigenic FGF19 analogue, significantly inhibited bile acid synthesis, reduced steatosis, hepatic inflammation and fibrosis in patients with NASH. Here we report the effect of aldafermin on NITs in phase 2 studies in patients with NASH.
Method: In part 1 of the study, 82 subjects were randomized to aldafermin 3 mg (n = 27) or 6 mg (n = 28) vs. placebo (n = 27) as a daily SC injection for 12 weeks. In part 2 of the study, 94 subjects received open-label aldafermin 0.3 mg (n = 23), 1 mg (n = 49) or 3 mg (n = 22) for 12 weeks for dose-range finding. Key inclusion criteria included biopsy-proven NASH with NAS ≥ 4 (at least 1 point in each component), Stage 1–3 fibrosis and absolute liver fat content (LFC) by MRI-PDFF ≥ 8%. APRI, FIB-4, fatty liver index (FLI) and ratio of triglyceride and HDL (TG/HDL) were evaluated at baseline (BL) and week 12 (W12).
Results: At BL, mean APRI, FIB-4, FLI and TG/HDL values were similar across all groups. At W12, aldafermin-treated patients showed reductions in NITs of fibrosis (APRI and FIB-4) and fatty liver (FLI) (Table 1). In contrast, no improvement was seen with placebo-treated subjects. Improvements were observed as early as 2 weeks on aldafermin and were maintained throughout treatment duration. TG/HDL ratio decreased significantly with aldafermin treatment.

Table 1: Change from baseline to week 12 in non-invasive tests.

	APRI	FIB-4	FLI	TG/HDL
Part 1: Double-Blind, Placebo-Controlled				
PBO	0.03	0.08	0.3	−0.7
Aldafermin 3 mg	−0.24***	−0.14	−1.2	−0.9
Aldafermin 6 mg	−0.17***	−0.01	−2.2	−1.3**
Part 2: Open-Label				
Aldafermin 0.3 mg	−0.14*	−0.04	−2.2	−0.9
Aldafermin 1 mg	−0.38***	−0.22**	−3.1***	−1.4***
Aldafermin 3 mg	−0.44***	−0.35**	−2.7	−1.7***

***p < 0.001, **p < 0.01, *p < 0.05 vs baseline.

Conclusion: Aldafermin therapy produced improvements in several simple and inexpensive NITs of liver fibrosis, steatosis and cardiovascular risk. These NITs may be useful for monitoring early treatment response to aldafermin.

FRI048

Evaluating the patient-perceived impact of non-alcoholic steatohepatitis with compensated cirrhosis

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Background and Aims: NASH-CHECK is the first patient-reported outcome measure (PROM) developed specifically for patients with non-cirrhotic non-alcoholic steatohepatitis (NASH; fibrosis F1-F3) in accordance with the US Food and Drug Administration guidance for PROMs supportive of drug labelling claims. It contains items assessing symptoms and health-related quality of life (HRQOL; activity limitations, emotions and lifestyle items). The current study assessed the symptom burden and HRQOL impacts experienced by patients with compensated cirrhotic NASH and compared them to the concepts covered by NASH-CHECK.
Method: A qualitative study with concept elicitation interviews was conducted with compensated cirrhotic NASH patients attending hepatology clinics in the United States and United Kingdom. Thematic analysis identified key symptoms and HRQOL impacts. These were compared with the key concepts encompassed by NASH-CHECK. New symptom items identified were discussed with an international group of clinicians to gain consensus on their relevance to compensated cirrhotic NASH.
Results: Thirty-three patients were interviewed, 61% female, mean (SD) age = 64.5 (7.8) years, body mass index = 34.5 (4.1). Comorbidities included type II diabetes 81.8%, obesity 87.9%, and hypertension 39.4%. Saturation was reached during the thematic analysis. Key symptoms identified in NASH-CHECK (pain, bloating, itch, fatigue, sleep, cognitive) were all reported. Key HRQOL concepts identified in NASH-CHECK (activity limitations, emotional, social, relationships, and work impacts) were also frequently reported and found to be comprehensive in relation to patients' experience of NASH with compensated cirrhosis. Additional symptoms reported included muscle cramps 54.6%, generalised pain 42.4%, shortness of breath 42.4%, and heartburn 39.4%. On clinical review, these additional symptoms identified were deemed to be related to co-morbidities or medication side-effects and so not directly related to compensated NASH cirrhosis or appropriate for inclusion in a PROM.
Conclusion: NASH patients with compensated cirrhosis experience similar symptoms and HRQOL impacts to patients with earlier stages of disease but may experience them more severely. These data suggest that NASH-CHECK is likely to be applicable in the compensated NASH cirrhosis population. Cognitive debriefing interviews are being conducted to further evaluate NASH-CHECK in cirrhotic patients.

FRI049

Systematic review and meta-analysis of FIB-4 for the diagnosis of advanced fibrosis due to non-alcoholic steatohepatitis

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Background and Aims: Liver biopsy is the current standard for the staging of fibrosis in patients with nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH). However, biopsy is expensive, invasive, and not ideal for monitoring of fibrosis. Due to these limitations, noninvasive tests (NIT) have been developed, including the fibrosis-4 index (FIB-4), which includes age, platelets, and serum ALT and AST. Our objective was to summarize the evidence regarding the diagnostic performance of FIB-4 for staging fibrosis in NAFLD/NASH using a systematic literature review (SLR) and meta-analysis (MA).
Method: Searches were conducted in MEDLINE and Embase to identify studies published in English from 1/1/1945–3/21/2019, that evaluated the diagnostic performance of FIB-4 to stage fibrosis in patients with NAFLD/NASH. Methods followed the PRISMA guidelines. Random effects meta-analyses (restricted maximum likelihood approach) were conducted on diagnostic odds ratios (DOR) in terms of the logit of sensitivity and specificity with a focus on biopsy-confirmed advanced fibrosis (F3-4 vs F0-2) at the FIB-4 cut-points of <1.30 and ≥ 2.67.
Results: The SLR identified 42 studies including 31,309 patients with NAFLD/NASH. FIB-4 cutoffs ranging from 1.30 to 3.25 yielded the best performance to stage fibrosis (AUROCs 0.80–0.95, n = 25 studies). Except for five studies with poor to moderate performance (AUROCs 0.52–0.65), FIB-4 showed good to excellent accuracy for diagnosing any fibrosis (biopsy-confirmed F1-4 vs F0, AUROCs 0.70–0.95, n = 34). FIB-4 performed best at predicting advanced fibrosis (F3-4 vs F0-2; AUROCs 0.80–0.95, n = 17) or cirrhosis (F4 vs F0-3, AUROCs 0.78–0.92, n = 4), compared with significant fibrosis (F2-4 vs F0-1, AUROCs 0.62–0.84, n = 8). MA results from nine studies including 8,155 patients (Figure) suggest that FIB-4 was a strong predictor of advanced fibrosis using both cut-points with slightly higher DOR for the cut-point ≥ 2.67 in comparison with <1.30 (DOR of 9.93 vs. 8.04).

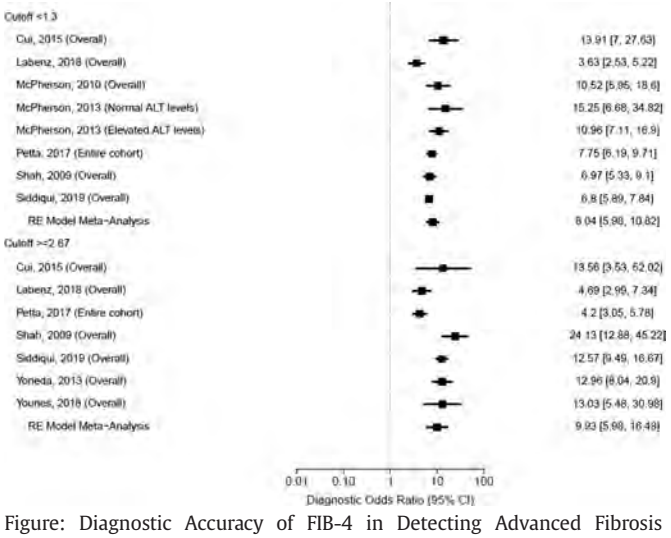

Figure: Diagnostic Accuracy of FIB-4 in Detecting Advanced Fibrosis by Cutoff. Abbreviations: CI = confidence interval; FIB-4 = fibrosis-4 index; RE = random-effects.

Conclusion: This SLR and MA shows that FIB-4 is an accurate NIT of advanced fibrosis in patients with NAFLD/NASH. MA results show that diagnostic accuracy may be best at the FIB-4 cut point ≥2.67 for advanced fibrosis. Further research is needed to determine what patient and setting characteristics that may impact the accuracy of FIB-4.

FRI050

Liver incytes: assessment of fibrosis and steatosis in patients and healthy volunteers

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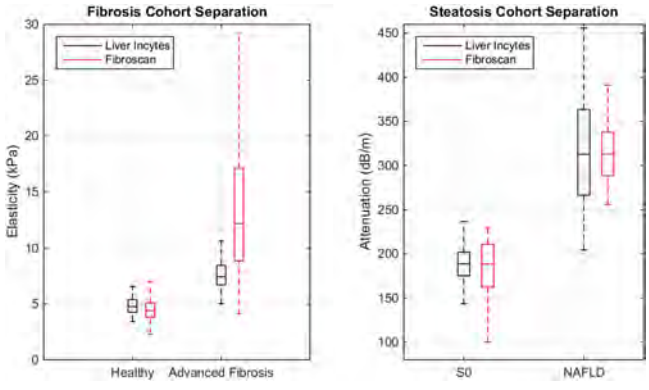
Background and Aims: Non-invasive liver fibrosis and steatosis measurements have been shown to allow better disease staging and clinical management and are correlated to patient outcomes. Here we present initial fibrosis and steatosis measurement results using Liver Incytes, a volumetric ultrasound elasticity and attenuation measurement system. The aim was to evaluate the ability of Liver Incytes to discriminate between healthy volunteers (HV) and those with clinically diagnosed non-alcoholic fatty liver disease (NALFD) or previous Hepatitis C virus (HCV).
Method: Liver Incytes is a steatosis and elasticity measurement system (Sonic Incytes, BC, Canada) comprising an ultrasound transducer and a vibration device to generate multi-frequency (40–70 Hz) steady state shear waves in the patient. The ultrasound elasticity and attenuation is measured over a volume of the liver, using an intercostal approach. Volumes are collected in a fan of 30 degrees, at a depth of 15 cm. Patients and HV were recruited from three clinical sites in the United States and Canada. HV had no history of liver disease. Patients were enrolled with either NALFD or HCV. Patients had a FibroScan® (FS) of greater than 8 kPa. FS was completed on the same day for comparison. The ability of Liver Incytes to discriminate HV from those with advanced fibrosis or steatosis was measured using Area Under the Receiver Operating Curve (AUROC). A subset of patients also had Magnetic Resonance Elastography (MRE) and Proton Density Fat Fraction (MR-PDFF).
Results: A total of 50 HV and 48 patients were recruited. The mean [range] age of the volunteers was 27 [19–58] years and 61 [31–75] for patients. 27 of the patients had clinically diagnosed NAFLD and 21 had HCV post SVR. Median [IQR] stiffness for the HV was 4.8 [1.1] and 7.5 [1.7] kPa for patients on Liver Incytes and 4.4 [1.3] and 12.5 [9.0] kPa when measured with FS. Mean attenuation for the HV and patients was 200 [61] and 298 [98] respectively on Liver Incytes and CAP score was 210 [59] and 295 [96] on FS respectively. The AUROC for Liver Incytes was 0.964 for fibrosis and 0.985 for steatosis, using FS as the gold standard.
Seven patients participated in the MR sub-study. When looking at elasticity, the concordance correlation coefficient was 0.80 for Liver Incytes and 0.20 for FS. The Pearson's coefficient between attenuation and MR-PDFF was 0.98 for Liver Incytes and 0.73 for FS.



Conclusion: Initial results show that Liver Incytes is able to discriminate HV from patients with advanced fibrosis and steatosis. Initial concordance and correlation with MRE and MR-PDFF were superior for Liver Incytes compared to FS although numbers are small. Larger clinical trials should be undertaken.

FRI051

Analysis of the prevalence of metabolic syndrome components and other factors as predictors of disease progression among an urban population with NAFLD and/or NASH

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Background and Aims: The incidence and prevalence of NAFLD/NASH is rising globally, as is the incidence of metabolic syndrome. The spectrum of NAFLD ranges from simple steatosis to non-alcoholic steatohepatitis with variable degrees of liver fibrosis, cirrhosis and HCC. Current literature illustrates an association between NAFLD and comorbid conditions such as diabetes, obesity and dyslipidaemia. The aim is to determine whether the components of metabolic syndrome and other relevant comorbid conditions/factors can predict a disease progression of NAFLD and/or NASH in an urban population.
Method: Retrospective review of 2764 patient charts at the Toronto Liver Centre with an indicated NAFLD and/or NASH diagnosis. 1968 patient charts with complete demographic information and comorbid condition history were included. Four components of metabolic syndrome: diabetes, obesity, dyslipidemia, hypertension and other factors/comorbid conditions including elevated liver enzymes, coronary artery disease (CAD) and AST:ALT ratio (>0.8) were examined.
Results: Of the 1968 patient charts, 1140 male patients (58%) and 828 female patients (42%). In terms of age distribution: <30–37, 30 to 39–168, 40 to 49–409, 50 to 59–612. 60–69–460, 70 to 79–206, 80 to 89–69, 90 to 99–7. The components of metabolic syndrome and other comorbid condition/diagnostic measures were examined individually across the fibrosis stage scale *(see* Figure 1*)*. In addition, they were assessed collectively to determine whether an association exists between disease progression and the number of components. The mean number of factors that patients had at each fibrosis stage was: F0: 1.77; F0-F1: 2.03; F1: 2.30; F1-F2: 2.35; F2: 2.70; F2-F3: 2.51; F3: 2.70; F3-F4: 3.06; F4: 3.32. The most commonly observed number of factors (mode) at each fibrosis stage was as follows: F0: 1; F0-F1: 2; F1: 2; F1-F2: 2; F2: 2; F2-F3: 2; F3: 3; F3-F4: 4; F4: 4.

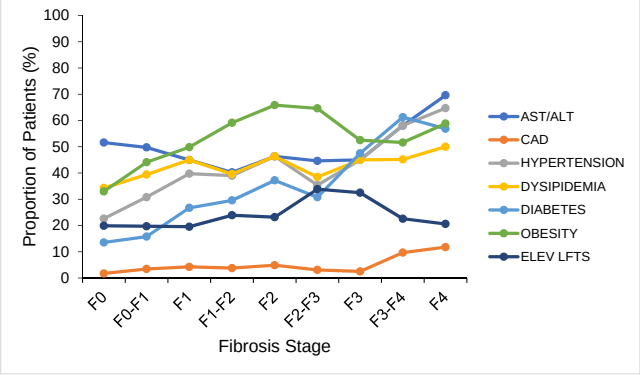

Figure 1: Proportion of patients with each individual component of metabolic syndrome/relevant study factor at defined fibrosis stages (n = 1968).

Conclusion: There is a relatively strong positive correlation between disease stage and the proportion of patients diagnosed with diabetes and hypertension. To a lesser degree, a positive correlation was also observed for obesity and dyslipidaemia (Figure 1*)*. Individually, these factors appear to be good predictors of disease progression. Most people with severe fibrosis (F4) have diabetes, diabetes (56.9%), obesity (58.8%), dyslipidaemia (50.0%) and hypertension (64.7%). On average, there is some indication that advanced fibrosis is associated with a greater number of components of metabolic syndrome/relevant study factors compared to lower stage fibrosis when only considering the extreme ends of fibrosis (F0 and F3 to F4) and not the intermediate stages.

FRI052

The impact of ethnicity on incidence of NAFLD/NASH among patients referred to the Toronto liver centre for non-invasive evaluation with transient elastography

Justin Lee[1], Anish Jammu[1], Hamed Dallali[1], Sirajuddaula Kausar[1], Muhammad Khurram[1], Silva Cortez[1], Marzena Magnes[1], Magdy Elkhashab[1]. [1]*Toronto Liver Centre, Toronto, Canada*
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Background and Aims: The prevalence of NAFLD/NASH is rising in North America and worldwide. The etiology of NAFLD is multifactorial with environmental factors and dietary habits considered as major contributing factors. Genetic factor and ethnicity play a major role as well. We sought to investigate the impact of ethnicity on prevalence of NAFLD among a cohort of patients with multiple ethnic backgrounds, referred to the Toronto Liver Centre for evaluation with transient elastography (Fibroscan®).
Method: 2219 patients referred for evaluation of liver stiffness were reviewed. All patients had fatty liver disease with no other underlying liver condition. Each patient was labeled with their closest ethnic origin. Fibrosis scores were average to eliminate ambiguity in judgment for scores that lie between two numbers (F1-2 = 1.5). An age range of 5 years was used incrementally for each cluster, starting from 1939–1998. As such, only individuals over age 21 were considered in this retrospective study.
Results: Of the total 2199 viable patients, 673 patients were of Asian descent, 207 were of Hispanic origin, 304 of East European background, 722 West European and 293 Middle Eastern. The level of fibrosis was particularly elevated for those of Hispanic/Latino origin in older age. As a general observation, the West European cohort had greater average fibrosis scores than any other ethnicity over the 50 year. A spike in fibrosis scores in the 1945–1950 age range was also noted for all ethnicities. However, this was especially pronounced in East European, Middle Eastern and Asian groups. It was apparent that those groups only developed greater fibrotic severity once the certain age is reached. This is indicated by the sharp incline in the 1945–1950 age groups. On the contrary, the West European population demonstrated a positive linear slope starting from the earlier age groups. Although the greatest number of NAFLD patients stem from the 1959–1962 age groups, the average fibrosis scores collected from this group led to a trough rather than a crest in the graph (Figure 1).

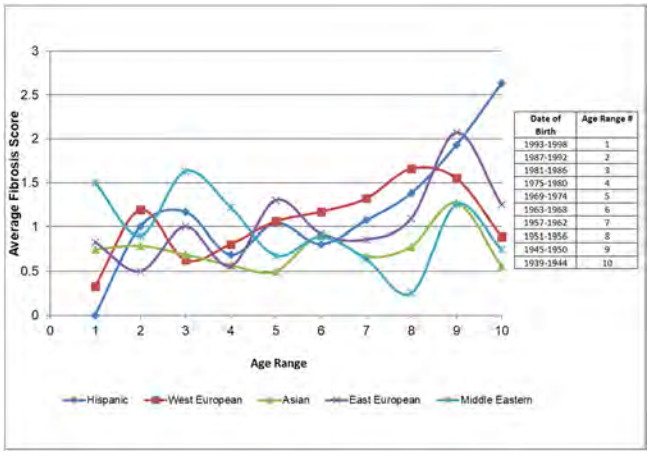

Figure 1: Average fibrosis scores relative to closest ethnic background.

Conclusion: There is probable indication to suggest a relation between ethnicity and the level of fibrosis at certain age ranges. This is particularly reflected in the Hispanic patient cohort, in which only patients in the 1957–1962 age range and above began to develop significant fibrosis. As for Asian and East European groups, although there is deviation in the actual fibrosis score values, the general trends were similar. This indicates that the difference between these two groups lie in the overall average fibrosis score itself, rather than the trend of development.

FRI053

Drivers of diagnosis and referral decisions in non-alcoholic fatty liver disease patients

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD), including non-alcoholic steatohepatitis (NASH), is an increasing cause of chronic liver disease. NAFLD patients frequently suffer from metabolic syndrome and are at higher risk of NAFLD progression and cardiovascular mortality. The aim of this focused review was to assess the current state of awareness of specialists and general practitioners (GPs) on the epidemiology of NAFLD in adults and to identify the factors responsible for the diagnosis and treatment of NAFLD.
Method: Two independent reviewers conducted a search via PubMed, Embase, and DynaMed on studies published between 2005–2019, following a pre-defined Patient, Intervention, Comparison, Outcome (PICO) model. Final accepted studies were summarized and applied to pre-determined research questions related to the study aim.
Results: Twenty-two systematic reviews and network meta-analyses of randomized clinical trials were included. Physician and patient awareness: Many GPs seem to lack knowledge of NAFLD and underestimate its prevalence, e. g. 70% in Italy and 84% in USA. Similarly, patient awareness of NAFLD is also very low, even among those with relevant risk factors such as obesity (19% in an USA study). Likewise, 94% of diabetes specialists in UK report that their patients are not aware of NAFLD and 66% are concerned about missing a diagnosis of severe NAFLD. Diagnosis and screening: More than half of GPs do not test their NAFLD patients for other common causes of fatty liver. In USA, specialists, but not GPs, are more likely to screen patients with diabetes for NAFLD and NASH (68% vs. 44%), but less likely to screen patients with abdominal pain (7% vs. 24%, respectively). Additionally, endocrinologists and cardiologists report greater clinical concern regarding NAFLD and are more likely to refer patients than GPs (67% vs. 33%).
Conclusion: Many patients at risk of NAFLD are currently missed due to inadequate screening and uncertainties surrounding diagnostic tests and treatment options, along with lack of knowledge related to screening and management.

FRI054

Validation of the accuracy of the fast score for detecting non-alcoholic steatohepatitis patients at high risk of becoming cirrhotic in a North American cohort

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Background and Aims: Management of patients with nonalcoholic steatohepatitis liver disease who are at elevated risk of progressing to cirrhosis (at risk NASH) would be enhanced by an accurate noninvasive diagnostic test. The new FAST™ score, a mix of FIBROSCAN™ and aspartate aminotransferase (AST), has shown moderate diagnostic accuracy for at-risk NASH (area-under-the-Receiver-Operating-Characteristic [AUROC] = 0.80) in European cohorts. Our aims were to validate the FAST™ in a North American cohort and show how its accuracy might vary by patient mix.
Methods: We studied 585 adults with biopsy-confirmed NASH from the multicenter NASH Clinical Research Network (CRN) cohort. At-risk NASH was defined as definite NASH, NAFLD Activity Score (NAS) ≥ 4 and a fibrosis stage ≥ 2. We used the echosens® formula for FAST™ from liver stiffness (E kPa), steatosis (controlled attenuation parameter [CAP] dB/m), and AST (U/L); the FAST™-based Rule-Out (FAST™<0.35, sensitivity = 90%) and Rule-In (FAST™ >0.67, specificity = 90%) zones. The diagnostic performance measures used were AUROC, sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV); these were calculated for the total sample and by subgroups of patients and by FIBROSCAN™ exam features.
Results: The NASH CRN population was 38% male, 79% white; 73% obese; with means for age = 51 years, ALT = 66 U/L, and AST = 50 U/L. The prevalence of at-risk NASH was 37% vs. 50% in the Derivation population. The AUROC of FAST™ for at-risk NASH in the NASH CRN was 0.81 (95% CI: 0.77, 0.84), very similar to the AUROC in the Derivation population: 0.80. The Se, Sp, PPV and NPV are shown in the Table. The performance of FAST™ was better in non-whites vs. whites (AUROC: 0.91 vs 0.78; p = 0.0002) and inversely related to obesity status (AUROC: 0.94 in normal, 0.84 in overweight, and 0.78 in obese; p = 0.04). No differences were observed by other patient characteristics, or FIBROSCAN™ exam features.
Table: Diagnostic accuracy of FAST™.

Populations	Prevalence of at- risk NASH	Rule-Out Zone Zone intervals FAST™ <0.35	Gray Zone FAST™ 0.35–0.67	Rule-In Zone FAST™ >0.67
Derivation	50% (174/350)	% patients: 31% Se = 0.90 Sp = 0.53 NPV = 0.85	% patients: 40%	% patients: 29% Se = 0.48 Sp = 0.90 PPV = 0.83
NASH CRN	37% (214/585)	% patients: 35% Se = 0.91 Sp.0.50 NPV = 0.90	% patients: 38%	% patients: 27% Se = 0.51 Sp = 0.87 PPV = 0.69

Conclusion: FAST™ for diagnosing at-risk NASH was validated in large, multi-racial population from North America. Diagnostic performance varies by subgroups of NASH patients, including race, obesity, and prevalence of at-risk NASH.

FRI055

Serum lipidomic landscape of non-alcoholic fatty liver disease progression to hepatocellular carcinoma in a Caucasian population

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is a highly prevalent (24% of population globally) and progressive liver disorder emerging as a leading risk factor for hepatocellular carcinoma (HCC). The molecular mechanisms behind the progression from NAFLD to HCC (NAFLD-HCC) remain elusive, and surveillance of 'at risk' NAFLD patients constitutes a clinical challenge. In this study, we elucidate the deregulated metabolic serum landscape of NAFLD-HCC patients and individual lipids diagnostic utility.
Method: We have performed comprehensive ultra-high-performance liquid chromatography mass spectrometry (UHPLC-MS), investigating 1,295 metabolites in 196 serum samples from Caucasian patients with biopsy-proven diagnosis stratified into healthy and obese (CTRL = 44), metabolic disease (NAFLD = 93), NAFLD-HCC (n = 27) and alcohol or viral-associated HCC (AV-HCC = 32).

	CTRL vs NAFLD-HCC	NAFLD vs NAFLD-HCC	AV-HCC vs NAFLD-HCC
Model	0.989	0.997	0.999
AFP	0.786	NA	0.613
ALT	0.776	0.733	0.570

Results: In total, we detected 470 metabolites, including amino acids, their derivatives and lipids. We identified two major metabolic events in NAFLD-HCC. The initial metabolic rearrangement occurs in the onset of NAFLD (healthy liver; obese to NAFLD), characterized by differential expression (FDR $p < 0.05$) of 232 metabolites (DEMs). The most prevalent metabolites impaired within the first metabolic step include amino acids, acylcarnitines (AC), bile acids, cholesteryl esters, and glycerophosphocholines. Contrary, the significantly augmented metabolic program covers mostly free fatty acids (FFA), as well as diglycerides and triglycerides (TG). The second metabolic rearrangement was observed at the neoplastic conversion from NAFLD to NAFLD-HCC. The late metabolic switch included major metabolic aberrations covering 334 DEMs with significant changes in AC, ceramides and FFA. The progressive change (Spearman, $p < 0.05$) of metabolites showed gradual TG increase, progressive loss of AC and complete deterioration of FFA as the main perturbed metabolite subclasses. Multivariate analysis discriminated NAFLD-HCC patients from CTRL, NAFLD and HCC with a different etiology (AV-HCC) (Q2 = 0.51, R2 = 0.57). We generated ROC curves for DEMs and built a discriminator model including the top 5 metabolites, reaching a predictive accuracy >90%. The predictive power of the panel is superior to alpha-fetoprotein (AFP) and biochemical marker alanine transaminase (ALT) for the liver function:
Conclusion: Serum metabolomics revealed a specific perturbation of the lipid biology during the progression from healthy liver and morbidly obese, through NAFLD to malignant onset of NAFLD-HCC. Our metabolite panel can be clinically exploited in surveillance of patients at risk for developing HCC (morbidly obese, diabetic and NAFLD patients), and can distinguish NAFLD-HCC from AV-HCC.

FRI056

Difference between antinuclear antibody-positive non-alcoholic steatohepatitis and autoimmune hepatitis based on differential patterns of peripheral T lymphocytes

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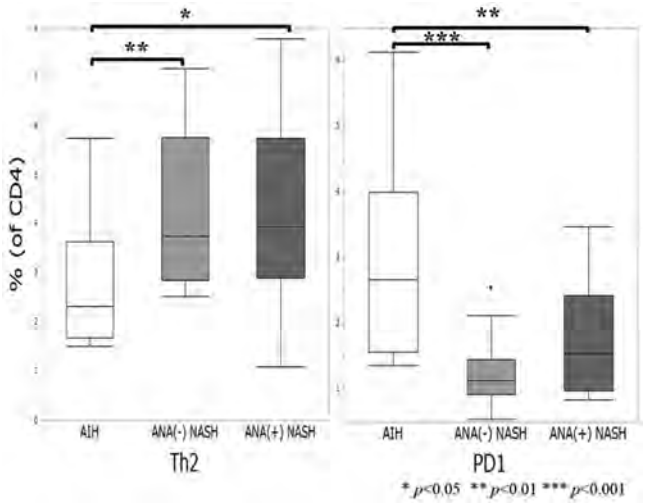
Background and Aims: About 15–45% of nonalcoholic steatohepatitis (NASH) has been reported to be seropositive for antinuclear antibody (ANA), and may be misdiagnosed as autoimmune hepatitis (AIH). Clinically, pathological diagnosis by liver biopsy is useful to discriminate ANA-positive NASH from AIH, but on some clinical situations, urgent medication by steroids without pathological diagnosis is needed, which may exacerbate the pathogenesis of NASH. NASH is known to involve immunological mechanism which is probably different from AIH, therefore it is possible that there are some differences in patterns of peripheral lymphocytes. The aim of this study is to determine differential patterns of peripheral T lymphocytes between ANA-positive NASH and AIH.
Method: Peripheral blood mononuclear cells (PBMCs) were obtained from 38 patients pathologically diagnosed as NASH (ANA negative: positive = 21: 17) by liver biopsy, and also from 15 patients pathologically diagnosed as AIH, based on diagnostic criteria of AIH (Hennes EM, et al. Hepatology 2008). For flow cytometry analysis, we used several subset markers of T lymphocytes to select target T lymphocytes. All T cells were selected from PBMCs through CD3 gating, and helper T cells (Th) and cytotoxic T cells (CTL) were selected through CD4 and CD8 gating, respectively. To further separate Th, we used CXCR3+CCR4-CCR6- (Th1), CXCR3-CCR4-CCR6+ (Th2), CXCR3-CCR4+CCR6+ (Th17), and CD25+CD127- (Treg) as Th subset markers. Furthermore, PD1 and CTLA4, recently focused as immune tolerance, were also examined. T lymphocyte percentages were calculated as standardized by CD3, CD4, and CD8 positive cells with each gating.



Results: We found no differences in the percentages of all T cells, Th and CTL between ANA-positive NASH and AIH patients. Among Th cells, ANA-positive NASH patients showed a significant higher percentage of Th2 compared to AIH patients, but we found no differences in the percentages of Th1, Th17 and Treg. Concerning PD1 and CTLA4, ANA-positive NASH patients showed a significant lower percentage of CD4+PD1+ T cells compared to AIH patients. On the

other hand, we found no differences in the percentages of CD8+ PD1+ and CTLA4+ T cells.
Conclusion: This study suggests that ANA-positive NASH is different from AIH in patterns of peripheral T lymphocytes, in particular, Th2 and CD4 + PD1 + T cells. The underlying mechanism for this difference remains to be elucidated, but this differential pattern may be useful to noninvasively discriminate ANA-positive NASH from AIH.

FRI057
Utility of metabolomic biomarkers to identify non-alcoholic fatty liver disease in liver transplant recipients
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Background and Aims: Nonalcoholic fatty liver disease (NAFLD) is a rising indication for liver transplantation (LT) worldwide. Diagnosis of recurrent NASH after LT requires liver biopsy, which is invasive, costly, and impractical for serial monitoring. Our aim was to use an unbiased, noninvasive metabolomics approach to identify biomarker profiles for nonalcoholic fatty liver (NAFL) and steatohepatitis (NASH) in LT recipients.
Method: This cross-sectional pilot study included 39 LT recipients who underwent liver biopsy and had simultaneous plasma samples collected and analyzed using ultra-high-performance liquid chromatography – mass spectrometry (UHPLC-MS) to elucidate metabolomic profiles. The resulting profiles were compared between patients with recurrent NAFL/NASH vs. normal liver (negative control) and acute rejection (positive control).
Results: Univariate analysis revealed 22 metabolites that were differentially and significantly ($p < 0.05$) altered in patients with recurrence of NAFLD compared to patients with normal liver histology on biopsy. Three metabolites (triglyceride (44:1), triglyceride (53:0), and arginine) were identified as potential specific markers of NAFLD vs. both normal and rejection biopsies. Within participants with NAFLD, 15 metabolites were identified as divergent between NAFL and NASH. Among patients transplanted for NASH cirrhosis, 18 metabolites were significantly altered between those with fibrosis vs. without fibrosis on liver biopsy.

Conclusion: In conclusion, we were able to identify a number of potential metabolic biomarkers that could be used in the clinical setting to noninvasively identify recurrent NAFL and NASH. Further investigation with a larger sample size is warranted to validate these preliminary results.

FRI058
Cost-effectivity analysis of several non-invasive test strategies for detection and referral of patients with non-alcoholic fatty liver disease at risk of advanced fibrosis
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Background and Aims: Non-alcoholic fatty liver diseases at risk of advanced fibrosis is underdiagnosed out of hepatology clinics. Strategies based on education, tools and communication with primary care could impact on the management of this entity. The main aim was to compare the effectiveness of several non-invasive test son detection and referral of patients with NAFLD at risk of advanced fibrosis.
Method: Peer-to-peer sessions were scheduled with all primary care centres from Virgen del Rocio University Hospital. Hepamet Fibrosis Score (HFS), NAFLD Fibrosis score (NFS) and FIB4 were available to be requested from primary care. Combined score was defined as gold standard for advanced fibrosis risk detection. Combined score was

Class	Metabolite	Code OWL	NASH *vs.* NAFL	
			log_2 (fold-change)	Student´s *t*-test (*p*-value)
AA	Lysine	AA15	-0.37	5.08E-03
ST	androsterone sulfate + etiocholanolone sulfate	ST08	-1.97	2.52E-02
	isomer pregn-5-ene-3,20-diol sulfate	ST10	0.81	9.62E-03
LPE	PE(22:4/0:0)	MAPE35	0.84	3.84E-02
	PE(22:5/0:0)	MAPE38	0.72	4.05E-02
PC	PC(15:0/18:2)	DAPE06	-0.63	4.25E-02
	PC(16:0/19:1)	DAPE12	-0.31	1.37E-02
	PC(17:0/18:1)	DAPE11	-0.53	4.70E-02
	PC(17:0/18:2)	DAPE14	-0.66	3.17E-02
	PC(17:1/18:1)	DAPE13	-0.77	1.92E-02
	PC(17:0/20:3)	DAPE25	-0.70	2.78E-02
	PC(P-16:0/20:4)	MEMAPC19	-0.78	1.95E-02
	PC(P-17:0/20:4)	MEMAPE14	-0.83	3.43E-02
LPC	PC(0:0/15:0)	MAPC05	-0.62	4.54E-02
SM	SM(d18:2/20:0)	SphLip_17	-0.64	2.74E-02

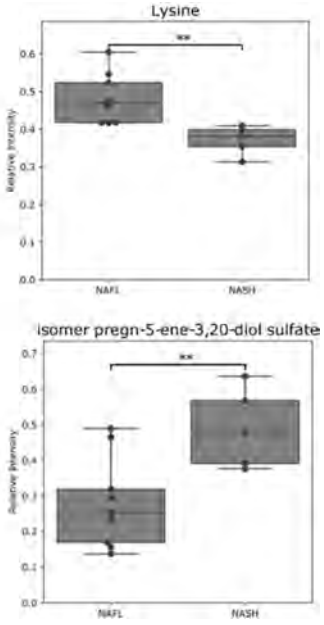

Figure: (abstract: FRI057): Metabolites found to be significantly ($p < 0.05$) altered in the comparison NASH *vs.* NAFL. Two representative boxplots are displayed. Abbreviations: AA, amino acid; ST, sterol; LPE lysophosphatidylethanolamines, PC, phosphatidylcholines; LPC, lysophosphatidylcholines, SM, sphingomyelins.

built adding 0,1 or 2 points from each NIT when under or over lower or higher cut-off from 0–6 points. Patients at risk of advanced fibrosis were defined when combined score was ≥3 points. Diagnostic accuracy and cost-effectiveness was calculated. Confidence intervals and Odds ratio were also calculated.

Results: Eight-hundred and fifty requests from primary care. T2DM 23%; Obesity 47%; Normal ALT 40%; females 40%. Patients at risk of advanced fibrosis were: NFS: 37.9% (322/850); FIB4: 39.6% (337/850) y HFS un 17.5% (197/850). CS was suggestive of advanced fibrosis (CS ≥ 3) in 116/850 cases (13.6%). Referral rate was lower with HFS in comparison with NFS (OR:0,35, IC95%:0,28–0,44) and FIB4 (OR:0,32, IC95%:0,26–0,40). Cost of these three analyses were: 0,70€ in diabetics and 1.85€ in non-T2DM. Besides, average cost of hepatology clinics attendance of a patient with NAFLD has been calculated around 570.78€ (Sánchez-Torrijos et al. 2019). The cost of the management of this cohort could be 485.163€, but referring based on HFS >0.12 (N = 149) Cost: 85.046€ (IC95%:72.645–97.448); NFS > −1.455 (n = 322) Cost: 183.791€ (IC95%:167.969–199.613); FIB4>1.30 (n = 337) Cost: 192.353€ (IC95%:176.398–208.308).

Conclusion: Implementation of a detection and referral strategy based on Hepamet fibrosis score increased diagnostic accuracy and is cost-effective saving a half of the budget.

FRI059

Prediction of advanced fibrosis with transient elastography is superior to gut microbiota-based approaches in non-alcoholic fatty liver disease

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Background and Aims: The presence of liver fibrosis is the major determinant of future liver related complications in patients with non-alcoholic fatty liver disease (NAFLD). Several studies identified associations between gut bacterial dysbiosis and liver fibrosis. Based on these findings, microbiome signatures have been explored as prediction models for advanced fibrosis in NAFLD. The aim of this study was to validate and directly compare the diagnostic performance of gut microbiota-based machine learning approaches to other simple and widely used non-invasive tools for the prediction of advanced fibrosis.

Method: 16S rRNA gene sequencing was performed in a well-characterized cohort of 96 biopsy-proven NAFLD patients. Random Forest models based on clinical data and sequencing results were compared to transient elastography, the NAFLD fibrosis score and the FIB-4 index.

Results: A Random Forest model containing clinical features and gut bacterial taxa achieved an area under the curve (AUC) of 0.87 for the prediction of advanced fibrosis (Fig. 1a). The model was only marginally superior to a similar model without microbiota features (AUC 0.85). The model that aimed to validate a published algorithm that used whole genome sequencing, achieved an AUC of 0.71 with less than half of species being resolved based on 16S rRNA gene sequencing (Fig. 1b). AUCs for the NAFLD fibrosis score and FIB-4 index were 0.86 and 0.85, respectively (Fig. 1c). Transient elastography performed best with an AUC of 0.93 (Fig. 1c).

Conclusion: A gut microbiota signature might help to predict the presence of advanced fibrosis. However, transient elastography, which is a fast and convenient method, achieved the best diagnostic performance for the detection of NAFLD patients at risk for disease progression.

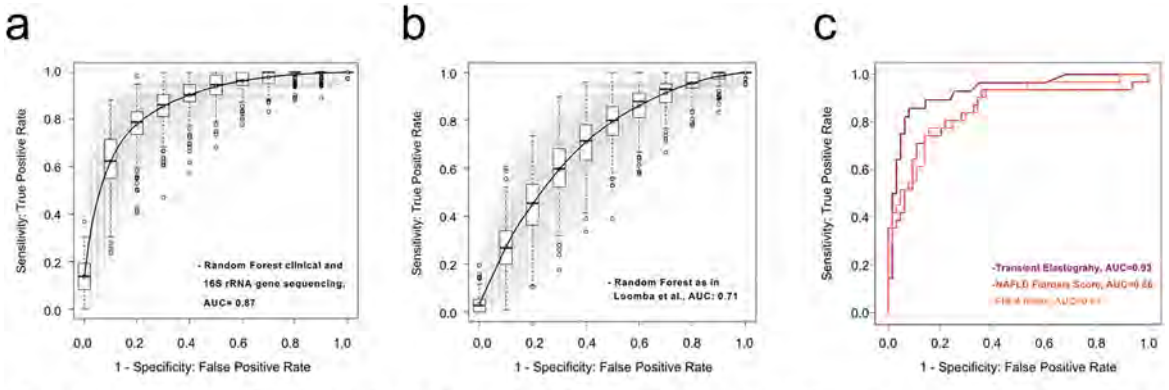

Figure legend: (a) Area under the curve (AUC) for our Random Forest model based on 14 features that were identified by Random Forest feature elimination. Light grey lines represent the 300 training runs, the black line and AUC represent the median over these. (b) AUC for the validation in approximation of the Random Forest model by Loomba et al. (c) Performance of the FIB-4 index, NAFLD fibrosis score and transient elastography. In a-c, 65 patients were staged as F0-F2 and 31 as F3-F4.

Figure: (abstract: FRI059)

FRI060

The accuracy of the fast score in predicting NASH with significant fibrosis

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Background and Aims: Vibration controlled transient elastography (VCTE) is useful in assessing steatosis via its controlled attenuated parameter (CAP) and fibrosis measured as liver stiffness. Recent data showed that the FAST score which uses a formula that contains the CAP, stiffness and Aspartate Aminotransferase values is highly accurate in predicting non-alcoholic steatohepatitis (NASH) patients who have NAS score of ≥ 4 and Fibrosis ≥ 2 (NAS4F2). We aimed to validate the FAST score and assess its performance in various patients' subgroups.

Method: This is a cross-sectional analysis from tertiary care center in the U.S. NAFLD was diagnosed based on society guideline recommendations. NASH was assessed via Kleiner's histology score. Liver biopsy was done within 6 months from VCTE (FibroScan, Echosens, France) and patients were excluded if they had >5% change in body weight. M and XL probes were chosen based on the automated machine recommendation.

Results: To date, 101 patients have been enrolled with an average age of 57.2 years and body mass index (BMI) of 31.0 kg/m^2. Of those 55% had NASH,21% had F0, 24% had F1, 16% had F2, 12% had F3 and 27% had F4. The average FAST score for the entire cohort was 0.5. The FAST score was accurate in predicting NAS4F2 with a corresponding AUC of 0.74. We then analyzed the FAST score by various sensitivity and specificities cut offs as well as the Youden's index (Table 1). Finally, we assessed if there are any differences in the FAST score in predicting NAS4F2 by diabetes status or BMI. We found no difference in the accuracy for the FAST score in predicting NAS4F2 in diabetic's vs non-diabetics (AUC = 0.71 vs 0.73; p = 0.8182). We found no difference in the accuracy of the FAST score in predicting NAS4F2 in patients with BMI ≤ 30 kg/m^2 vs those >30 kg/m^2 (AUC = 0.73 vs 0.74 p = NS), but the accuracy varied between very good in patients with BMI ≤ 32 kg/m^2 (AUC = 0.73) to excellent in those >32 kg/m^2 (AUC = 0.82) and similarly in those with BMI ≤ 35 kg/m^2 (AUC = 0.73) and >35 kg/m^2 (AUC = 0.81).

Prevalence of NASH +NAS ≥ 4 +F ≥ 2	AUC [95% CI]	Description	Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy
30%	0.74 [0.63;0.84]	80%-Sensitivity	0.41	80%	52%	41%	86%	61%
		90%-Sensitivity	0.28	90%	37%	38%	91%	53%
		80%-Specificity	0.74	49%	81%	52%	79%	71%
		90%-Specificity	0.84	30%	90%	60%	76%	72%
		Max. of Yourdon's index	0.62	65%	69%	47%	82%	68%

Conclusion: The FAST score is an accurate score in predicting NAS4F2. FAST doesn't vary by diabetes status and its accuracy ranges between very good to excellent depending on BMI.

FRI062

Expanding the use of the vibration controlled transient elastography in morbid obese patients: validation of a new automated adaptive measurement depths algorithm in a large pooled NAFLD cohort

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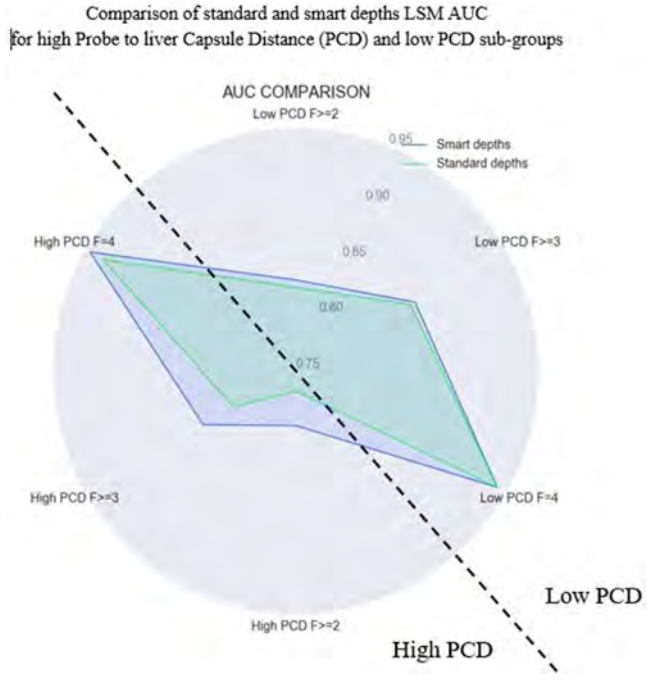
Background and Aims: The XL probe significantly expanded the applicability of VCTE (FibroScan), yet there are still challenges in morbidly obese (body mass index, BMI >40 kg/m²) patients when the probe to liver-capsule distance (PCD) is larger than the current maximum measurement depth (35–75 mm). Our objective was to evaluate a new automated adaptive measurement depths algorithm called 'smart depths' allowing Liver Stiffness Measurement (LSM) with the XL probe up to 45–85 mm and from 25–65 mm to 30–70 mm M probe in three pooled cohorts of patients investigated for suspicion of NAFLD.

Method: Patients underwent LSM and liver biopsy (LB). LB was scored in a blinded manner by two expert pathologists using the NASH CRN scoring system. To be included patients needed an interpretable LB as well as a valid FibroScan examination (defined as at least 8 valid measurements) with both Standard and 'Smart Depths' stiffness measurement. To avoid spectrum bias when comparing patients with high and low PCD, median PCD determined for each fibrosis stage were used to split the cohort into two groups; low PCD and high PCD. Diagnostic performance was assessed using area under the ROC curves (AUC) and compared using Delong test.

Results: 669 patients (348 UK, 202 USA, 119 France) were included (BMI = 36 ± 7 kg/m², age = 52 ± 12 years, 52% male, PCD 23 ± 5: mm). For each fibrosis stage, patient distribution and median PCD were as follows: F0: [40%; 20.6 mm], F1: [26%; 24.1 mm], F2: [14%; 22.6 mm], F3: [15%; 21.9 mm] and F4: [5%; 23.3 mm]. Sub-groups consisted of 339 (BMI: 39 ± 7.2 kg/m²) and 330 patients (BMI: 32 ± 5.6 kg/m²) with high and low PCD, respectively. In low PCD sub-group, diagnostic performances of standard stiffness versus Smart Depths were equivalent, with respective AUCs as follows: F ≥ 2AUC = 0.819/0.825 (p = 0.006); F ≥ 3AUC = 0.859/0.863 (p = 0.008) and F = 4 AUC = 0.941/0.941 (p = 1). In the high PCD sub-group, diagnostic performance was significantly improved by the Smart Depths with: F ≥ 2AUC = 0.767/0.795 (p = 0.0001); F ≥ 3AUC = 0.809/0.838

(p = 0.00008) and F = 4 AUC = 0.933/0.946 (p = 0.007) for standard/Smart Depths, respectively (Figure). Moreover, LSM applicability increased by 13% in the high PCD sub-group using the Smart Depths.



Conclusion: The performance of LSM as a fibrosis surrogate marker is improved in high PCD patients by automatically adjusting the depth of measurement to the patient morphology. This will need to be confirmed in a prospective study.

FRI063

A diagnostic approach of non-alcoholic fatty liver disease with a machine learning model using parameters derived from ultrasound B-mode examination

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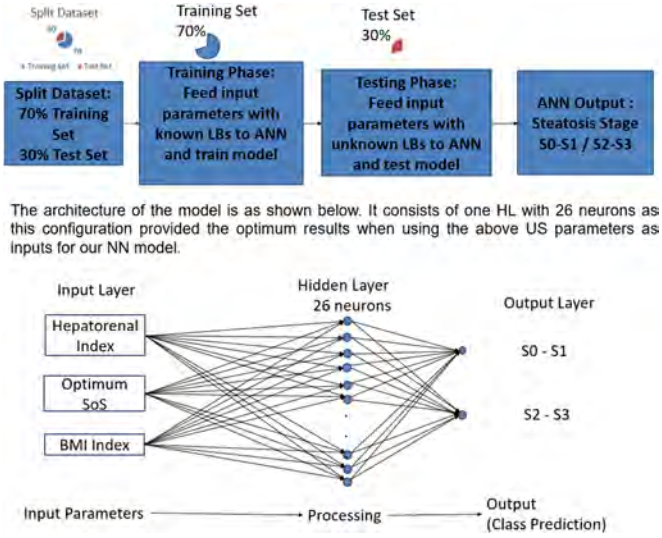
Background and Aims: Non-Alcoholic Fatty Liver Disease (NAFLD) may lead to Non- Alcoholic Steatohepatitis (NASH) and to cirrhosis and liver failure. Ultrasound (US) is widely used for the disease diagnosis and staging. The aim of this study is to build a Neural Network (NN) model to evaluate the impact of B-Mode US examination parameters for Steatosis assessment.
Method: 195 liver biopsy-validated for Steatosis patients (117 S0-S1 and 78 S2-S3) were included in our study. To calculate the Hepatorenal Index (HI) a B-Mode US examination was performed by an expert radiologist on each patient's right lobe, including view of the right kidney at the same depth. The examiner provided a diagnostic impression of each patient's Steatosis (0–3). The input features selected were the Body Mass Index (BMI), the HI and optimum speed of sound index (SSI), calculated from a US B-Mode image showing each patient's liver parenchyma. These parameters were used as input to a NN classifier. Our dataset was divided into training and testing sets (70%-30% of whole dataset). For the training process a three-fold cross validation (CV) was used. In order to have a robust estimation of the model's performance the split of the dataset and training-testing process was repeated 30 times.
Results: The classifier had a mean CV accuracy of 87.53% with 95% confidence interval (CI) 87.44% –87.62%. The mean accuracy of test sample was 89.44% (95% CI: 89.31%–89.56%). The mean Area Under Curve (AUC) for test sample was 0.953 (95% CI: 0.944–0.962). The radiologists' diagnostic impression accuracy against the liver biopsy for the whole dataset was 80%.



Conclusion: The NN classifier performance was superior to the radiologists' estimation and can be used as a supplementary tool in liver steatosis assessment.

FRI064

Predicting advanced fibrosis using non-invasive clinical tests and modern machine learning methods in TARGET-NASH

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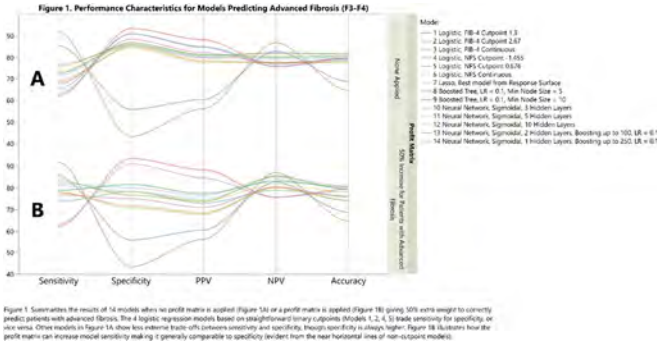
Background and Aims: Liver biopsy is the reference standard for fibrosis staging, but is an invasive procedure with limitations and potential complications. There is an unmet need for readily-available noninvasive tests (NITs) to identify patients with advanced fibrosis. The aim of this study is to describe the performance characteristics of NITs in predicting advanced fibrosis using modern machine learning methods and real-world data from TARGET-NASH.
Method: TARGET-NASH is a longitudinal observational study that includes patients with NAFLD defined by biopsy or pragmatic case definitions. NITs, including the Fibrosis-4 (FIB-4) index and the Non-Alcoholic Fatty Liver Disease Fibrosis Score (NFS) that were calculated within 6 months of liver biopsies were analyzed in predictive models. Individual variables of the FIB-4 and NFS were considered for the models: age, BMI, diabetes, albumin, platelets, ALT, AST, as well as composite FIB-4 and NFS scores. Performance characteristics were calculated for predictive models including logistic regression, lasso, boosted trees, and neural networks. A profit matrix was then applied to the models, prioritizing the diagnosis of advanced fibrosis.
Results: 859 adult patients with a liver biopsy and both FIB-4 and NFS were included in this analysis. Median age was 57 and 60% of the patients were female. 86% of the subjects were Caucasian, 60% had diabetes and median BMI was 33 kg/m^2. Median ALT and AST were 49 IU/L and 41 IU/L, respectively. Median platelet count was 201 × 10^3

and median albumin was 4.2 g/dL. Median FIB-4 score was 1.66 and NFS score −0.29. Performance characteristics based on a validation sample of 25% of the patient cohort are in Figure 1A. Figure 1B shows that defining a profit matrix is effective at increasing sensitivity. Most neural network models provide a good balance between sensitivity and specificity for predicting advanced fibrosis, with 3 of these models (Models 10, 11, 14) providing sensitivity and specificity ≥ 78%. The lasso model has similar performance with greater interpretability for the impact of individual covariates.



Conclusion: Analyzing the individual component variables for commonly-used NITs provide a good balance between several performance characteristics for predicting advanced fibrosis using modern modeling techniques. However, this improved performance may come at the expense of less easily-interpretable models, or may require applications to classify patients based on their data.

FRI065

Liver derived apoptotic microparticles as biomarkers to detect transition from simple steatosis to steatohepatitis in non-alcoholic fatty liver disease

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Background and Aims: Microparticles (MPs) are small membrane-derived vesicles that are shed from cells to act as biological messengers regulating biological processes. Liver derived MPs are ASGPR positive (Asialoglycoprotein receptor) alone or in combination with others markers such as EPCAM (Epithelial cell adhesion molecule) and CD133 (Prominin-1), both of them overexpressed in hepatic progenitor cells. The aim of the study was to analyze the role of liver derived MPs in non-alcoholic fatty liver disease (NAFLD) progression.

Method: Thirty-four patients with NAFLD proven liver biopsy were included; simple steatosis (n = 10) and steatohepatitis scored by SAF score (n = 24); F0-F1 (n = 12); F2 (n = 11) and F3-F4 (n = 11). MPs were determined in heparin plasma by Flow cytometry by size (0,2–1 µm-Megamix Plus SC protocol, BD) and phosphatidylserine measured by Annexin V+. Cellular origin was determine using ASGPR, EPCAM and CD133.

Results: Patients with steatohepatitis (n = 24) showed significantly higher levels of MPs expressing AV+ASGPR+ (561.7 ± 88.9 vs. 1593.7 ± 393.2; p = 0.025), AV+EPCAM+ (318.4 vs. 1149 ± 195.3; p = 0.007), AV ± EPCAM+ASGPR+ (18.3 ± 12.4 vs. 70.1 ± 19.6; p = 0.025), AV +EPCAM+CD133+ (130.7 ± 33.3 vs. 834.2 ± 147.6; p < 0.001 and triple markers combination AV+EPCAM+ASGPR+CD133+ (3.1 ± 1.9 vs. 33.7 ± 13.4; p < 0.001). Triple markers combination reached the highest diagnostic accuracy segregating simple steatosis from steatohepatitis [AUROC = 0.917; (IC95%: 0.797–1); p = 0.001, sensitivity; 0.947 and specificity: 0.714]. There were no differences between MPs quantification and fibrosis stage. Quantification of liver-derived microparticles were also significantly different in patients with or without lobular inflammation and with or without ballooning.

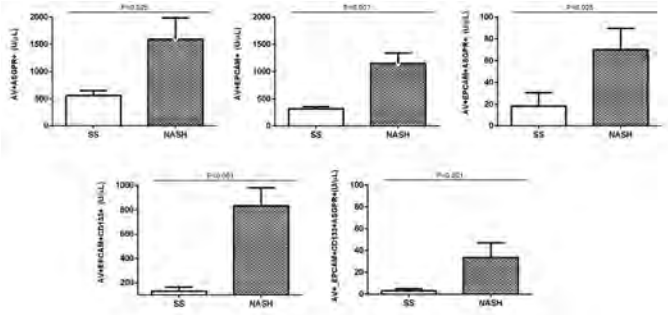

Figure 1: Levels of MPs (Data are represented as Means± SE)

Conclusion: Liver-derived microparticles increased in patients showing inflammation, ballooning and steatohepatitis irrespective of fibrosis stage. Identification and quantification of liver-derived microparticles could be a useful biomarker to detect the transition from simple steatosis to steatohepatitis in non-alcoholic fatty liver disease.

FRI066

Obeticholic acid improves hepatic fibroinflammation as assessed by multiparametric magnetic resonance imaging: interim results of the regenerate trial

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Background and Aims: A month-18 interim analysis of REGENERATE showed that treatment with OCA improved fibrosis and steatohepatitis based on liver histology in patients with NASH.[1] However, liver biopsy has several limitations and development of noninvasive tools for diagnosis and monitoring of NASH is warranted. Here, we evaluate the effects of OCA on multiparametric magnetic resonance imaging (MRI)-derived iron-corrected T1 (cT1) mapping which is thought to correlate with hepatic fibroinflammatory disease (Wilman 2017) and has been shown to predict clinical outcomes (Jayaswal 2018).

Method: Multiparametric MRI by Liver *MultiScan* (Perspectum Diagnostics, UK) was performed in a subset of REGENERATE NASH patients with fibrosis stage 2 or 3 (N = 20) randomized 1:1:1 to placebo (n = 7), OCA 10 mg (n = 6) or OCA 25 mg (n = 7). Change in cT1, a standardized imaging biomarker of hepatic fibroinflammatory disease, as well as change in liver fat content was evaluated following 18 months of treatment.

Results: At baseline, mean (SD) cT1 was similar across all 3 treatment groups (856.7[106.8]ms; 943.2[116.11]ms; and 882.1 [94.75]ms in placebo, OCA 10 mg and OCA 25 mg groups, respectively), with values in the elevated range reflective of a population with definite

steatohepatitis and significant fibrosis. Following 18 months of treatment, a dose dependent reduction in cT1 was observed with a mean change from baseline of –91.7 ms in the OCA 25 mg group and –59.6 ms in the OCA 10 mg group, compared to –1.4 ms in the placebo group. Mean liver fat content at baseline was 16.29% (placebo), 19.27% (OCA 10 mg) and 15.3% (OCA 25 mg). Modest reduction (–7.9%) in fat content was noted in the OCA 25 mg arm as early as 6 months following treatment, and was generally sustained through Month 18.

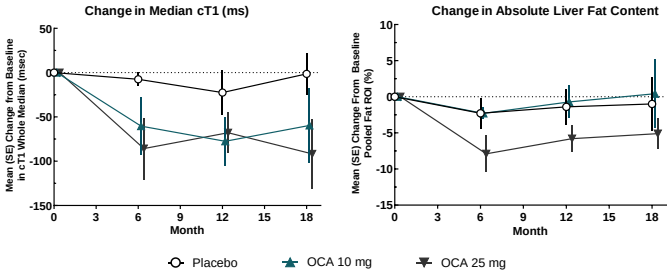

Figure: Fibroinflammatory Disease and Fat Content by Multiparametric MRI.

Conclusion: Treatment with OCA resulted in dose-dependent improvements in cT1 and liver fat content measured noninvasively by multiparametric MRI, that may be consistent with histologic improvements in steatohepatitis and fibrosis, as well as in serum-based noninvasive markers of steatohepatitis and fibrosis. (Anstee 2019)

1. The REGENERATE month 18 interim analysis results are based on surrogate endpoints considered reasonably likely to predict clinical benefit and longer term OCA treatment effect on clinical outcomes has not yet been demonstrated: the study is ongoing through outcomes to characterize OCA's clinical benefit

FRI067

Liver stiffness measurement by fibroscan predicts the occurrence of liver-related events and death in patients with NAFLD-related compensated advanced chronic liver disease

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Background and Aims: Patients with advanced fibrosis related to nonalcoholic fatty liver disease (NAFLD) are at risk of developing hepatic and extrahepatic complications. Liver stiffness measurement (LSM) by FibroScan has a good diagnostic accuracy for advanced fibrosis in patients with NAFLD, and can also predict the occurrence of liver-related events in patients with chronic hepatitis C. Data about the accuracy of LSM in the prediction of events in NAFLD, especially in patients with NAFLD and F3-F4 fibrosis, are scarce. We investigated whether, in a large cohort of patients with NAFLD and compensated advanced chronic liver disease (cACLD), LSM at baseline, at follow-up, and its variations are accurate for the prediction of hepatic and extrahepatic events.

Method: We retrospectively evaluated consecutive individuals with NAFLD with histological diagnosis of F3-F4 fibrosis and/or LSM >10 KPa, and prospectively followed-up for at least 6 months. LSM was measured by FibroScan using M or XL probe, and recorded at baseline and within 1 year from the last follow-up visit. Difference between follow-up and baseline LSM (delta LSM) was categorized as <–20%, –20% to +20%. >+20%. Hepatic (liver decompensation –ascites, encephalopathy, variceal bleeding and jaundice- and hepatocellular carcinoma (HCC)) and extrahepatic (cardiovascular and extrahepatic cancers) events, as well as overall and liver-related death were recorded during follow-up.

Results: 937 patients (56.5% males, mean age 60.2 years, mean BMI 32.5 Kg/m2, 61.1% with diabetes, 78.6% with cirrhosis) with a median follow-up time of 37.9 months (1st/3rd quartiles 22.6/64.8 months) were enrolled. 67 (7.2%) hepatic decompensation, 34 (3.6%) HCC, 56 (6%) all-cause deaths and 33 (3.5%) liver-related deaths were recorded. By Cox regression analysis and after adjusting for age, gender (only for HCC), serum albumin and platelets levels, baseline LSM was independently associated with occurrence of hepatic decompensation (HR 1.03, 95%C.I. 1.02–1.04, $p < 0.001$), HCC (HR 1.02, 95%C.I. 1.00–1.04, $p = 0.01$), and liver-related death (HR 1.03, 95% C.I. 1.02–1.04, $p < 0.001$). In a subgroup of 494 patients with available follow-up LSM, delta LSM was independently associated with hepatic decompensation (HR 1.54, 95%C.I. 1.04–2.48, $p = 0.04$), together with baseline LSM (HR 1.03, 95%C.I. 1.00–1.05, $p = 0.01$), and with liver related death (HR 1.87, 95%C.I. 1.05–3.34, $p = 0.03$).

Conclusion: In patients with NAFLD and F3-F4 fibrosis baseline LSM can predict the occurrence of hepatic decompensation, HCC and liver-related death. Moreover, changes in LSM during follow-up can further help to identify patients at higher risk of hepatic decompensation and liver-related death.

FRI068

Glympse liver test for noninvasive monitoring of combination drug therapy in a rat model of non-alcoholic steatohepatitis (NASH)

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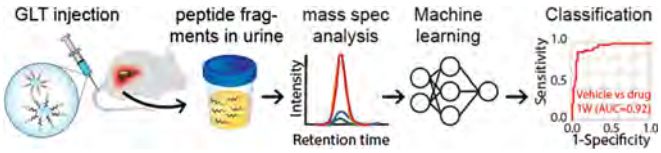
Background and Aims: NASH diagnosis is limited by invasive procedures. Glympse Liver Test (GLT) is an injectable mixture of 19 sensors that measure the activity of proteases in NASH progression and regression. Here, we analyze GLT's performance to noninvasively monitor the efficacy of a combination drug therapy in a rat model of NASH.

Method: Male Wistar Han rats fed a choline-deficient high fat diet (CDHFD) for 6 weeks were administered vehicle (n = 15) or a triple drug combination (ACC inhibitor, FXR agonist and ASK1 inhibitor, or TRIPLE; n = 15) for 6 more weeks while on CDHFD diet. Control rats received chow diet (CD, n = 10). GLT was administered i.v. at weeks 2, 4, 6, 7, 8, 10 and 12; urine was collected 120–180 min post-injection and analyzed by tandem mass spectrometry. Liver histology and RNAseq of liver tissue were also analyzed. Regularized logistic

regression algorithm was used for disease classification using gene or urine signals (using 80% train, 20% validation splits).
Results: Rats fed a CDHFD developed a wide range of liver fibrosis from low stages at 6 W (4 F0, 4 F1, 1 F2, 1 F3) up to cirrhosis at 12 W (5 F3 and 10 F4). In parallel, CDHFD rat had increased expression in 10 out of 13 human NASH proteases whose expression positively correlated with fibrosis stage (Pearson $\rho = 0.36–0.73$; padj <0.05). TRIPLE treatment significantly prevented fibrosis progression (3 F0, 9 F1, 2 F2, 1 F3) and reduced protease mRNA upregulation upon CDHFD. Training a classifier using biopsy-derived NASH protease gene expression allowed for discrimination of TRIPLE-treated animals with a perfect AUC = 1.00 and prediction of F2 and above (F2+) from F0-F1 with an AUC = 0.94. When testing GLT in this model, we efficiently predicted TRIPLE response non-invasively as early as 1 week after treatment initiation (AUC = 0.92) and staging of F2+ fibrosis over F0-F1 with an AUC = 0.90 (95% CI 0.79–0.97), outperforming biomarkers ALT, AST and PIIINP (AUROCs $\leq$ 0.77) in accuracy. GLT-predicted output probability of having F2+ also correlated with fibrosis stage. Urinary signal of probe 7, a cathepsin sensor, markedly increased in CDHFD rat at 6 and 12 W and decreased back to normal in TRIPLE-treated rats. Removing probe 7, decreased GLT performance to predict F2+ (AUC = 0.76) indicating that cathepsins are key contributors to disease classification.



Conclusion: GLT multiplexed sensors enable accurate staging of fibrosis in NASH and early monitoring of treatment response without the need for biopsy.

FRI069

Too many to refer? FIB-4 scores in primary care patients with abnormal liver tests

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Background and Aims: The Fibrosis-4 (FIB-4) Index has been proposed as a tool to improve the diagnosis and management of non-alcoholic fatty liver disease (NAFLD) in primary care patients at risk.[1–5] Our aim was to examine the FIB-4 score and its relationship with clinical components of metabolic syndrome (MetS) in a primary care population with abnormal liver tests and no other liver disease diagnoses.
Method: A retrospective study of electronic record data from a primary care clinic from 2007–2018 analyzed adult patients with abnormal liver tests for: (1) patient-level FIB-4 scores and the proportion of patients with values concerning for liver fibrosis (FIB-4 > 1.3) and cirrhosis (FIB-4 > 2.67); (2) demographic and clinical factors associated with a mean FIB-4 above these thresholds. Abnormal liver tests included any elevation in: bilirubin, transaminases, or alkaline phosphatase. Multivariable logistic regression models for the dependent variables of mean FIB-4 > 1.3 and mean FIB-4 > 2.67 were developed. Objective measures of MetS components served as independent variables: BMI (continuous), A1c > 6.5%, triglycerides >150 mg/dL, HDL < 50 mg/dL for women (<40 mg/dL for men), and blood pressure (BP) > 130/85 mm Hg.[2,3]
Results: 9,657 patients with 116,237 FIB-4 scores were included, with a median of 7 (IQR: 3–14) values per patient. Of these patients, 97.2% had at least one component of MetS, 8.4% had all five components, and 1.0% had an ICD-9/10 code for NAFLD. Using patient-level mean FIB-4 scores, 3,544 (36.7%) patients had values >1.3, and 555 (5.8%) >2.67 (Table 1). The logistic regression model identified male gender, Black race, elevated transaminases, elevated BP, hyperglycemia, hypertriglyceridemia, and hypothyroidism positively associated with a mean FIB-4 score >1.3. Similar results were found for the cirrhosis threshold.

Table 1: Proportion of patient-level FIB-4 scores exceeding clinical thresholds and odds ratios from regression models for the dependent variables of (1) mean FIB-4 >1.3 and (2) mean FIB-4 >2.67.

FIB-4 N = 9,657	% >1.3			% >2.67		
Mean	36.7%			5.8%		
Median	32.0%			3.8%		
Maximum	60.0%			20.8%		
Minimum	14.4%			1.3%		
	Mean FIB-4 >1.30 N = 3,547			**Mean FIB-4 >2.67 N = 564**		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Male	1.76	1.61–1.92	<0.01	1.63	1.37–1.95	<0.01
Black	1.31	1.20–1.43	<0.01	1.77	1.48–2.13	<0.01
Transaminase abnormality	1.74	1.57–1.92	<0.01	3.09	2.73–4.03	<0.01
BP >130/85	1.71	1.47–1.99	<0.01	1.47	1.08–2.02	0.02
A1C > 6.5%	1.25	1.12–1.39	<0.01	0.96	0.77–1.19	0.69
Low HDL	0.84	0.76–0.92	<0.01	1.36	1.12–1.65	<0.01
Triglycerides >150	1.15	1.05–1.27	<0.01	0.83	0.68–1.01	0.06
BMI	0.97	0.96–0.97	<0.01	0.96	0.94–0.97	<0.01
Hypothyroidism	1.26	1.11–1.42	<0.01	1.04	0.80–1.37	0.75

Conclusion: Many primary care patients with risk factors and clinical signals of NAFLD have FIB-4 scores concerning for advanced fibrosis. Future work is needed to validate the performance of FIB-4 in this setting.

FRI070

Circulating PCSK9 levels correlated with advanced disease in patients with biopsy-proven non-alcoholic fatty liver disease

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Background and Aims: Nonalcoholic fatty liver disease (NAFLD) has been associated with cardiovascular events, mainly in presence of NASH and fibrosis. Proprotein convertase subtilisin/kenin type 9 (PCSK9) is secreted into the plasma by the liver and regulates lipid homeostasis by promoting degradation of the LDL receptor and possibly lipogenesis, disrupting cholesterol homeostasis. In the present study we examined the effect of circulating PCSK9 levels on hepatic steatosis.
Method: Sixty-nine NAFLD biopsy-proven patients were recruited. Liver biopsies were classified by SAF score as Non-alcoholic fatty liver (NAFL) (n = 26) or as non-alcoholic steatohepatitis (NASH) (n = 43). Levels of circulating PCSK9 were evaluated by ELISA in 50 µl of serum samples.
Results: The half of NAFL group were males and 51% in the NASH (p = 0.588). Mean age was 48 ± 14 in the NAFL group and 55 ± 10 in the NASH group (p = 0.027). According to fibrosis stage; 43% of patients were F0, 16.5% were F1, 12.4% F2, 19.6% F3 and 7.2% F4. Levels of triglycerides were significantly higher in NASH compared to NAFL (109.73 ± 53.92 vs. 170.90 ± 77.61; p < 0.001) and levels of HDL cholesterol were higher in NAFL in comparison with NASH patients (59.06 ± 11.88 vs. 45.19 ± 11.69; p < 0.001), while levels of LDL

cholesterol (121.44 ± 28.54 vs. 105.46 ± 30.26) and total cholesterol (196.69 ± 34.54 vs. 180.26 ± 31.13) were similar between both groups (0.067 and 0.225 respectively). As shown in figure 1, PCSK9 in NASH patients was significantly higher than in NAFL group (p < 0.001). Patients without lobulillar inflammation (n = 6; 11.8%) had lower levels of PCSK9, than those with mild (n = 29, 56.9%) or moderate grade of inflammation (n = 16; 31.3%) (p = 0.014). On the other side, PCSK9 was lower in patients without ballooning (n = 21, 42%) than in those with mild (n = 24; 48%) or significant ballooning (n = 5; 10%, p = 0.001). Indeed, patients with fibrosis had higher levels of PCSK9 than those without (p = 0.004).

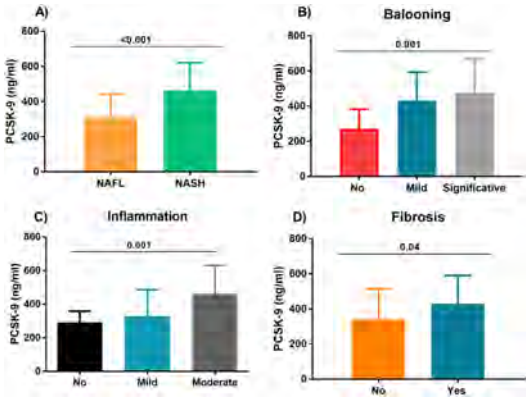

Figure 1: Data are shown as mean±SD. Circulating PCSK9 levels are increase in patients with NASH (a) ballooning (B), inflammation (C) and fibrosis (D).

Conclusion: Circulating PCSK9 levels correlated positively with fibrosis stage, ballooning and inflammation degree in patients with biopsy-proven NAFLD. Modulation of PCSK9 synthesis and release might be involved in NAFLD pathogenesis. PCSK9 could be a link between advanced NAFLD and cardiovascular risk.

FRI071

Non-invasive liver fibrosis markers, FIB-4, PRO-C3 and ADAPT, are significantly elevated in biopsy confirmed NAFLD patients at high risk of developing coronary heart disease and cardiovascular disease and are promising clinical decision making tools

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Background and Aims: A bidirectional association between NAFLD and cardiovascular disease (CVD) exists; as such CVD is the primary cause of mortality in NAFLD. Patients with advanced fibrosis (F3–4) are most at risk of clinical events and mortality. Currently, liver biopsy is used to diagnose and monitor patients. However, this is not suitable for mass screening. Hence, there is an urgent need for non-invasive markers. We aimed to investigate the association of non-invasive liver fibrosis tests and risk of developing atherosclerotic CVD (ASCVD) and coronary heart disease (CHD) over 10 years.
Method: Biopsy confirmed NAFLD patients had their risk of developing ASCVD and CHD estimated using ASCVD risk estimator and the Framingham Risk Score (FRS), respectively. Serum markers were determined at time of biopsy with PRO-C3 quantified by competitive ELISA. Patients were stratified into risk groups, patients with an ASCVD risk estimate and FRS ≥ 20% were considered high risk. Comparisons between high risk and low-moderate risk were assessed by t-test, area under receiver operating characteristic (AUROC) and logistic regression.
Results: 170 patients (mean age was 52, n = 72 male, n = 72 diabetic) were included. Those with F3–4 (n = 36) had significantly higher ASCVD and CHD risk estimates compared to patients with F0–2 (p < 0.0001 and p < 0.001 respectively). PRO-C3 correlated to both ASCVD and FRS risk estimates (Rho 0.36, p < 0.0001 and Rho 0.26, p < 0.001). Patients at high risk for ASCVD had significantly higher PRO-C3 levels compared to low-borderline risk (p < 0.002) with an odds ratio (OR) 1.04; PRO-C3 showed good discriminative ability (AUROC 0.73). High CHD risk patients had higher PRO-C3 levels compared to low risk (p < 0.02), AUROC 0.67 and OR 1.02. FIB-4 was significantly higher in those at high risk for ASCVD compared to low-borderline (p < 0.0001), AUROC 0.84 and OR 3.18. High CHD risk patients had greater FIB-4 levels than low risk (p < 0.0001), AUROC 0.75 and OR 1.28. ADAPT was greater in those at high ASCVD risk compared to low-intermediate risk (P < 0.0001), AUROC 0.88, OR 1.92. High risk CHD patients had greater levels of ADAPT compared to low- intermediate risk (p < 0.0001), AUROC 0.81 and OR 1.58.
Conclusion: NAFLD patients with a high risk of CHD and ASCVD have high levels of non-invasive fibrosis markers such as PRO-C3, ADAPT and FIB-4. PRO-C3 and ADAPT show promise as clinical decision-making tools and may have prognostic value.

FRI072

The FIB-8 score: validation of a model to screen patients with non-alcoholic fatty liver disease for significant fibrosis

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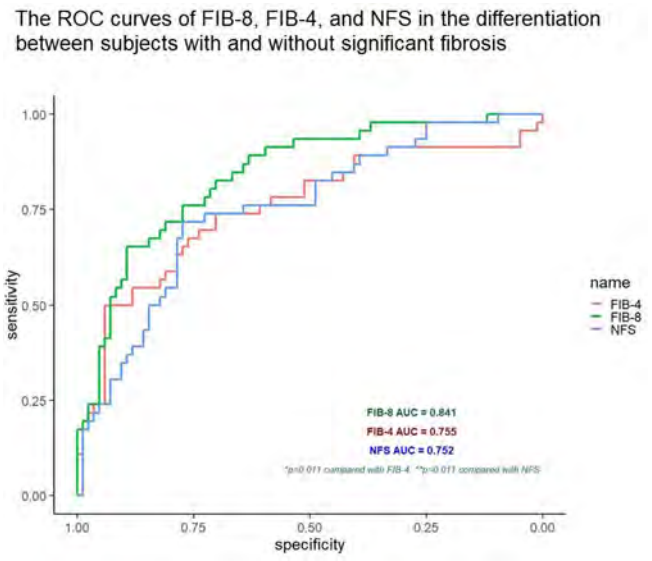
Background and Aims: Noninvasive fibrosis assessment is essential in the screening and diagnosis of non-alcoholic fatty liver disease (NAFLD). We have recently developed and validated (AASLD 2019 abstract #1723) a new model, FIB-8, optimized to detect clinically significant fibrosis (fibrosis stage 2, F2 or higher). In this study, we refine, field-test and validate the score in a real world cohort of NAFLD patients.
Method: FIB-8 was constructed to include four additional variables to FIB-4, namely, body mass index (BMI), albumin/globulin (A/G) ratio, gamma-glutamyl transferase (GGT), and diabetes (DM). The final FIB-8 model was as the following formula.
FIB-8 = FIB4 + 0.042*(BMI; if >40, use 40) - 1.314*(A/G ratio; if >1.5, use 1.5) + 0.004*GGT + 0.819*(DM; 1 if present)
In validating the model further, we analysed data in NAFLD patients who underwent magnetic resonance (MR) examination of the liver in our unit. Eligible patients had hepatic steatosis (proton density fat fraction>5%) without an alternate cause for the steatosis (e.g. heavy alcohol use). Liver stiffness ≥ 3.4 kPa was used to determine clinically significant fibrosis. Area under the receiver operating characteristic (AUROC) curve was used to evaluate the diagnostic accuracy of FIB-8, in comparison to FIB-4 and NAFLD fibrosis score (NFS).
Results: A total of 130 NAFLD patients were eligible for this validation. The mean age was 52.4 years, 53.1% were women, the mean BMI was 31.47 kg/m^2, and 34% had diabetes. Significant fibrosis was found in 35.4%. All had complete data for DM and for the calculation of FIB4, BMI, and A/G ratio. GGT was missing in 93 patients in whom linear imputation was used to render the data complete. In the Figure, the AUROC of FIB-8 was 0.84 with imputed data (n = 130) and 0.91 when only patients with complete data without imputation were included (n = 31). Either version of FIB-8 outperformed FIB-4 and NFS. The previously determined thresholds to rule out and rule in F ≥ 2(<0.72 and ≥ 1.92, respectively) had 97.8% sensitivity, 76.2% specificity, and 96.6% negative predictive value. When FIB-8 was used to diagnose advanced fibrosis (F3, liver stiffness ≥ 4.8 kPa), it also outperformed FIB4 and NFS (AUROC = 0.86 vs 0.80 and 0.77, respectively).



Conclusion: The new model (FIB-8) incorporating BMI, A/G ratio, GGT and DM into FIB4 yields higher accuracy to diagnose significant (F ≥ 2) and advanced (F ≥ 3) fibrosis compared to FIB-4 and NFS, when applied to real world patients undergoing MR evaluation. This simple score based on commonly available data may be used to select patients for further hepatological evaluation.

FRI073

Continuous CAP algorithm: reduced variability in a prospective cohort

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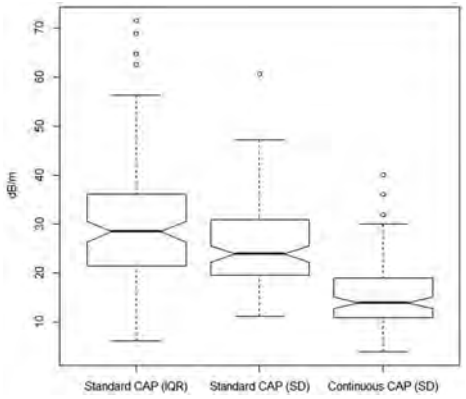
Background and Aims: Controlled Attenuation Parameter (CAP) is a surrogate marker of liver steatosis measured with FibroScan (FS) which was improved (named 'Continuous CAP') to reduce the variability. The aim is to evaluate the improvement on data collected during a clinical study in San Antonio, TX. Diagnostic performances of both (standard and continuous) CAP algorithms were assessed comparatively to the proton density fat fraction estimated by magnetic resonance imaging (MRI-PDFF).

Method: Patients referred for a routine cancer screening with no prior history of liver disease or alcohol abuse were offered participation in a prospective prevalence study. 113 consecutive patients (BMI = 30 ± 5 kg/m², age = 56 ± 8 years, 44% male) were enrolled with MRI-PDFF done within 86 days of FS examinations (78 with M and 35 XL FS probe). FS exams were performed by expert users. Continuous CAP results were obtained after reprocessing the raw ultrasonic data. Standard deviation and coefficient of variations were calculated and compared. Spearman's rank correlations and area under receiver operating characteristic (AUC) analysis of CAP versus MRI-PDFF were performed.

Results: For standard CAP, the reported values are median and interquartile range (IQR) (skewed distribution), while for continuous CAP we use mean and Standard Deviation (SD) (Gaussian distribution). In order to compare the variability between the two versions of the CAP, SD was also computed for standard CAP (Figure). The variability is improved by 61% (26 ± 9 dB/m and 16 ± 7 dB/m, standard and continuous CAP SD respectively). Coefficients of variation of less than 10% were obtained in 58% and 91% of exams for standard and continuous CAP, respectively. The correlation coefficients of MRI-PDFF versus CAP are 0.69 (standard) and 0.73 (continuous), which demonstrates an increased trueness of continuous CAP versus MRI-PDFF. AUC for CAP versus MRI-PDFF ≥ 5% (prevalence 31%) are respectively 0.889 [0.827–0.953] (standard)/0.900 [0.838–0.961] (continuous) with a p-value = 0.55). Cutoff are respectively 279 dB/m and 285 dB/m.



Conclusion: Continuous CAP demonstrates a reduced variability and increased correlation with the MRI-PDFF. These first results must be confirmed in a larger cohort of patients.

FRI074

Ultrasound small vessel imaging and deep learning; a novel approach to FLD screening

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Background and Aims: Fatty liver disease (FLD) affects approximately 30% of the global population and is associated with increased risk of developing hepatocellular carcinoma (HCC). Although primarily identified in patients with advanced liver disease, HCC is increasingly reported in non-fibrotic FLD. There is no effective screening for these patients. Hypoxia-driven neoangiogenesis and vascular changes play a key role in progression of both FLD and HCC, independent of fibrosis. We aimed to develop a method for non-invasive automated assessment of FLD and HCC based on intrahepatic vascular structures only.

Method: 95 participants were enrolled including: healthy volunteers (n = 19), early stage liver disease (n = 28), significant fibrosis (n = 27), and HCC (n = 21). Among those, 57 participants had FLD as underlying cause for their liver disease. All participants were subjected to an ultrasound-based method for visualising sub-millimetre intrahepatic vasculature using clinically available technology (contrast enhanced ultrasound and Doppler). A Deep learning classifier was trained on vascular images to differentiate healthy from diseased cases based on vascular features alone. Findings were correlated with clinical measures including liver stiffness measurements (LSM), controlled attenuation parameter (CAP), body mass index (BMI), plasma analysis of neoangiogenic factors, and an image quality score.

Results: The ultrasound-based vascular imaging was applied successfully in all cases, without any adverse event. The Deep learning classifier correctly labelled 88% of cases. Four healthy cases were mislabelled as diseased, two of which had raised CAP which could indicate early stage FLD. Seven diseased cases were mislabeled as healthy, these cases had lower LSM, CAP, and BMI compared to the correctly labelled cases, usually within the normal ranges, independent of image quality.

Figure: Image showing intrahepatic vascular structures with sub-millimeter resolution, segmentation, and skeletonisation.

Conclusion: Deep learning of ultrasound vascular imaging is able to correctly detect the majority of diseased cases, including early stage liver disease, suggesting that hypoxia-associated vascular changes occur in early stages of disease before fibrotic change. This method can be further developed to identify patients most at risk for FLD progression and HCC, without relying on fibrotic changes.

FRI075

Individual patient data meta-analysis on controlled attenuation parameter for the XL probe in obese patients

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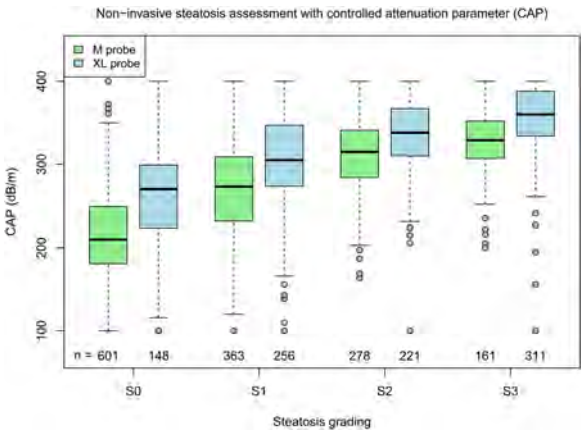
Background and Aims: Effective screening tools are important for detecting NAFLD and ruling out advanced fibrosis in obese patients. Ultrasound-based vibration controlled transient elastography (VCTE) with controlled attenuation parameter (CAP) is a promising tool that has been studied extensively in leaner patients of various aetiology. In the last few years, CAP has been included for the VCTE probe designed for use in overweight and obese patients (XL probe). CAP-XL has been tested in a number of studies, but consensus regarding cut-offs and diagnostic performance has not yet been reached. We, the international CAP-XL study group, performed an individual patient data meta-analysis to establish optimal cut-offs.

Method: A structured literature search yielded 15 papers that fulfilled the criteria of histology-controlled CAP analyses including the XL probe. We received data from 13 papers and finally included individual data from 2339 patients in the current analysis. Probe selection was based on automated probe selection tool, BMI or skin-to-liver-capsule distance, depending on the study. ROC analyses with optimization according to the Youden method were performed. For further details see the registered protocol (CRD42018099284).

Results: Patients (age 46 ± 14, 49% female) came from 20 centres in 9 countries and 3 continents. 29%, 23%, 47% were normal weight, overweight and obese, respectively. 52% had NAFLD/NASH, 12% ALD, 1% HBV, 9% HCV and 15% had other aetiologies. After taking appropriate probe selection into account, median CAP-XL values (n = 936) were higher than those from the M probe (n = 1403) at each steatosis grade, see Figure 1. This difference arises from higher prevalence of obesity in the XL probe population. The area under the curve (AUC) for distinguishing no steatosis (S0) from any steatosis (S1-S3) using the XL probe was 0.83 (95% CI 0.79 to 0.86). At the optimal cut-off of 294 dB/m sensitivity and specificity were 80% and 73% respectively. The corresponding AUC for S0–S1 vs S2–S3 was 0.78 (95% CI 0.75–0.81) and at the optimal cut-off of 306 dB/m sensitivity and specificity were 86% and 60%. Results in NAFLD patients alone are very similar.



Conclusion: For non-invasive grading of hepatic steatosis, median and optimal CAP values with the XL probe are higher than established ones for the M probe. The effects of covariates and implications for clinical practice have to be explored.

FRI076

Metabolomics approaches to identify biomarkers of non-alcoholic fatty liver disease

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Background and Aims: Nonalcoholic fatty liver disease (NAFLD) is a progressive liver disease that is strongly associated with type 2 diabetes. Accurate, non-invasive diagnostic tests to deliniate the different stages: degree of steatosis, grade of nonalcoholic steatohepatitis (NASH) and stage fibrosis represent an unmet medical need. In our previous studies, we successfully identified specific serum molecular lipid signatures which associate with the amount of liver fat as well as with NASH. Here we report underlying associations between clinical data, lipidomic profiles, metabolic profiles and clinical outcomes, including downstream identification of potential biomarkers for various stages of the disease.
Method: We leverage several statistical and machine-learning approaches to analyse clinical, lipidomic and metabolomic profiles of individuals from the European Horizon 2020 project: Elucidating Pathways of Steatohepatitis (EPoS). We interrogate data on patients representing the full spectrum of NAFLD/NASH derived from the EPoS European NAFLD Registry (n = 627). We condense the EPoS lipidomic data into lipid clusters and subsequently apply non-rejection-rate-pruned partial correlation network techniques to facilitate network analysis between the datasets of lipidomic, metabolomic and clinical data. For biomarker identification, random forest ensemble classification and neural network machine learning approaches were used to both search for valid disease biomarkers and to assess the relative improvement over clinical-data-only classification versus addition of our lipidomic and metabolomic datasets.
Results: We found that steatosis grade was strongly associated with (1) an increase of triglycerides with low carbon number and double bond count as well as (2) a decrease of specific phospholipids, including lysophosphatidylcholines. In addition to the network topology as a result itself, we also present lipid clusters (LCs) of interest to the derived network of proposed interactions in our NAFLD data from the EPoS cohort, along with our proposed biomarkers for various disease outcomes, as put forward by our current machine learning analyses.
Conclusion: Our findings suggest that dysregulation of lipid metabolism in progressive stages of NAFLD is reflected in circulation and may thus hold diagnostic value as well as offer new insights about the NAFLD pathogenesis. Using this cohort as a proof-of-concept, we demonstrate current progress in tuning the accuracy of neural network and random forest approaches with a view to predicting various subtypes of NAFLD patient using a minimal set of lipidomic and metabolic markers. A detailed network-based picture emerges between lipids, polar metabolites and clinical variables. Lipidomic/metabolomic markers may provide an alternative method of NAFLD patient classification and risk stratification to guide therapy.

FRI077

Optimal non-invasive screening strategy for non-alcoholic fatty liver disease in a prospective cohort of patients with type 2 diabetes

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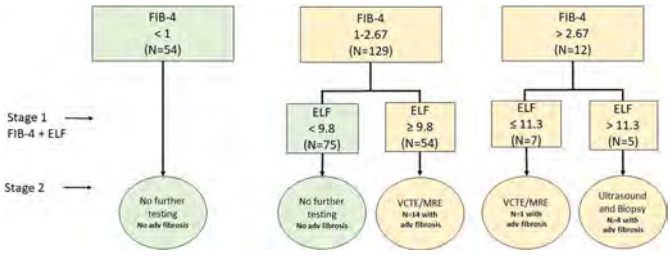
Background and Aims: Type 2 diabetes (T2DM) is associated with higher prevalence and severity of nonalcoholic fatty liver disease (NAFLD), therefore EASL guidelines recommend screening older patients with T2DM for NAFLD and advanced fibrosis. However, the optimal screening strategy is unknown. We hypothesized that the combination of FIB-4 and ELF would reduce the need for liver stiffness measurement (LSM), which is not typically available in primary care practices and aimed to define the optimal non-invasive screening strategy in T2DM patients.
Method: This interim cross-sectional analysis of a prospective cohort study included T2DM patients, age ≥ 50 years without an existing diagnosis of NAFLD. Exclusion criteria included other causes of chronic liver disease or hepatic steatosis including excessive alcohol use. Participants included in this study underwent a clinical history, physical exam, laboratory work-up including ELF, VCTE, MRI-PDFF and MRE. The primary outcome was the number of T2DM patients needing additional risk stratification with LSM after FIB-4 alone compared to a staged approach of FIB-4 and ELF.
Results: One-hundred ninety-five consecutive patients (42% men) with T2DM were included. The mean (±SD) age and BMI were 63.9 (±8.1) years and 30.5 (± 5.5) kg/m2, respectively. The prevalence of NAFLD (MRI-PDFF ≥ 5%) was 65% and 10% had advanced fibrosis (MRE >3.62 kPa). In a subset of 48 patients who underwent liver biopsy MRE accurately classified advanced fibrosis status in 42 (88%) patients. FIB-4 values of <1, 1–2.67 and >2.67 were present in 54 (28%), 129 (66%), and 12 (6%) of patients respectively. ELF scores of <9.8, 9.8–11.3 and >11.3 were present in 122 (63%), 61 (31%) and 12 (6%) patients respectively. Significantly fewer patients required LSM when combining FIB-4 and ELF (N = 61, 31%) compared to FIB-4 alone (N = 141, 72%), p < 0.001 (Figure) without misclassification of any patients with advanced fibrosis. In addition, the FIB-4 and ELF combination identified five high-risk patients with FIB-4 >2.67 and ELF >11.3, four of whom had advanced fibrosis on MRE and 1 with stage 2 fibrosis on liver biopsy.



Conclusion: The combination of FIB-4 and ELF is superior to FIB-4 alone in identifying low- and high-risk patients for NAFLD with advanced fibrosis in a screening cohort with T2DM and, if validated, the outlined approach to screening will increase the feasibility of screening T2DM patients for NAFLD and advanced fibrosis.

FRI079

Use of the fibrosis-4 score to estimate fibrosis stage for patients with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis in retrospective real-world datasets: a targeted literature review and feasibility assessment

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Background and Aims: It is not possible to classify patients with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH) by fibrosis stage in retrospective real-world datasets using International Classification of Diseases codes, because there are currently no specific codes to distinguish between different stages. The Fibrosis-4 (FIB-4) score could be used for retrospective staging because it requires variables that are available for most patients with liver disease in real-world datasets. A targeted literature review was performed to assess the evidence on the use of the FIB-4 score for staging fibrosis in NAFLD/NASH and to determine the optimal cut-off level(s) for stage 3 (F3) and stage 4 (F4) fibrosis.
Method: All published studies including use of FIB-4 score to assess fibrosis in adults with NAFLD/NASH, as well as select hepatitis C virus (HCV) publications, were reviewed.
Results: A total of 167 studies qualified for inclusion. Most concluded that FIB-4 is effective for detecting patients with NAFLD/NASH and advanced fibrosis (F3/F4) and most used cut-offs to identify these patients. The cut-off ≥ 2.67 was the most common and most validated, with an AUROC of ≥ 0.80 for predicting a high risk of advanced fibrosis in retrospective data in multiple studies. The next most common cut-off was ≥ 3.25, which was originally validated in patients with HCV. Very few studies classified patients into separate F stages prior to 3 recent studies that used 4 sets of cut-offs to distinguish between F3 and F4 patients (>2.67 or ≥ 3.25 for F3; >3.15, >3.5, or >4.12 for F4). The F4 cut-offs could not be traced to the NAFLD/NASH literature but >3.5 and >4.12 were identified as cut-offs for cirrhosis in 2 large HCV studies. These sets of cut-offs each selected significantly different populations in the NAFLD/NASH studies. Thus, currently, the 4 potential sets of cut-offs with the best rationale for identifying F3 and F4, respectively, are as follows: ≥ 2.67 and >3.5; ≥ 2.67 and >4.12; ≥ 3.25 and >3.5; ≥ 3.25 and >4.12.
Conclusion: FIB-4 score ≥ 2.67 is well-validated for identifying patients with advanced fibrosis. In terms of distinguishing between F3 and F4, the evidence is less strong. Studies aiming to classify patients into separate stages using FIB-4 are recommended to use more than one set of criteria as sensitivity analyses. Future validation studies to determine the optimal FIB-4 score cut-off/range for each stage would be welcomed.

FRI080

Obesity-specific health-related quality of life in patients with non-alcoholic steatohepatitis: results from the regenerate study

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Background and Aims: NASH patients typically are overweight or obese, which may negatively impact health-related quality of life (HRQOL). Weight loss may reverse NASH and may also improve HRQOL. We aimed to determine whether improvements in fibrosis and steatohepatitis with OCA were associated with improvements in Obesity-specific HRQOL in the month 18 interim analysis of REGENERATE.
Method: Obesity-specific HRQOL was assessed in non-cirrhotic NASH patients at baseline, 6, 12, and 18 months using Impact of Weight on Quality of Life (IWQOL) in REGENERATE. IWQOL is a validated self-reported questionnaire including five domains: Physical Function, Self-Esteem, Sexual Life, Public Distress, and Work, which range from 0–100 (higher score is better) and are averaged to calculate the total IWQOL score.
Results: 1,218 patients [age (mean ± SD) 54.1 ± 11.5 years, 57% female, 34% fibrosis (N = 411) stage 2 and 43% (N = 520) stage 3] were randomized to receive 10 mg (N = 407) or 25 mg (N = 404) of OCA or Placebo (N = 407). Balanced across 3 treatment groups and fibrosis stages, mean body weight and BMI were 95 ± 19 kg and 34.0 ± 5.6 kg/m^2, respectively; 75% and 37% of patients had a BMI>30 kg/m^2 and >35 kg/m^2, respectively. Baseline IWQOL scores were impaired in all domains, with a mean total score of 83.3 ± 17.4, similar in all groups. Treatment with OCA 25 and 10 mg was associated with a mean reduction from baseline to month 18 in body weight and BMI compared to Placebo: −2.17,−1.78,−0.68 kg and BMI −0.78, −0.63, −0.26 kg/m^2, respectively. Mean total IWQOL score showed a significant increase at month 6 (mean ± SD +1.4 ± 0.3), month 12 (+2.14 ± 0.35) and month 18 (+2.12 ± 0.40) compared to baseline ($p < 0.01$), driven by improvement of physical function, self-esteem and sexual life. Improvement was comparable across treatment groups and fibrosis stages over time (all $p > 0.05$), except for sexual life in OCA 25 mg at month 18 ($p < 0.02$). Achieving REGENERATE endpoints at month 18 was associated with greater mean IWQOL improvement: Fibrosis improvement 4.15+/−0.83 vs 1.7+/−0.45; NASH resolution 3.76+/−1.04 vs 1.86+/−0.43 (both $p < 0.05$)
Conclusion: Quality of life measured by IWQOL was impaired at baseline and improved in dose-dependent manner across treatment groups. To what extent these results are attributable to weight loss and to dose-dependent beneficial effects of OCA on fibrosis and NASH will be examined at the end of the study. The REGENERATE study remains ongoing and will continue through clinical outcomes for verification and description of clinical benefit

FRI081

Significant knowledge gap about non-alcoholic fatty liver disease (NAFLD) in real-world practices: a global survey of hepatologists, gastroenterologists, endocrinologists and primary care physicians

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Background: Despite being one of the most common causes of chronic liver disease, health-care providers' knowledge about NAFLD, its risk factors and management may vary across specialties. Our aim was to assess knowledge about NAFLD among 4 medical specialties, globally.

Methods: Surveys with 66 items divided in 4 domains (1. Practice Characteristic Domain: 10 items, 2. Knowledge of Disease Domain: 28 items, 3. Knowledge of Diagnostics Domain: 13 items, 4. Knowledge of Intervention and Management Domain: 15 items) were developed to assess physicians' knowledge (Table). For validity and accuracy, all questions and answers were reviewed by 8 hepatology experts. The IRB-approved survey was completed electronically by hepatologists (HEP), gastroenterologists (GE), endocrinologists (ENDO) and primary care/internists (PCP).

Results: 818 physicians (HEP = 264, GE = 297, ENDO = 69, and PCP = 188) from 14 countries completed the survey; practice duration 10 years (IQR 5–19); 72% hospital-based. HEPs saw the largest number of NAFLD patients/year, while PCPs saw the lowest: [HEP 140 (IQR 60–350), GE/ENDO 100 (50–300), PCP 20 (8–90), $p = 0.001$]. Disease knowledge (accurate classification of obesity/central obesity, importance of raised ALT, excessive alcohol threshold and the most common cause of death) were correctly identified more by GE/HEP than ENDO/PCP ($p < 0.001$). The role of diagnostic tests (ultrasound, transient elastography, and liver biopsy) was more accurately identified by GE/HEP than ENDO/PCP as was treatment management with life style modification and medications ($p < 0.01$). The use of practice guidelines was the most common method of acquiring new knowledge for all specialties (36% to 41%) followed by data from national/international conferences (HEP/GE/ENDO) while for PCP's Internet ranked second for knowledge (17%).

Table: Representative Questions Included in the Survey

1. Practice Characteristic Domain:
Primary practice setting (5 options)
Number of years in practice (write in option)
2. Knowledge of Disease Domain:
What is the prevalence of NAFLD in the general population in your country? (5 options)
Threshold of daily alcohol intake is used to rule out NAFLD in men (5 options)
Normal BMI and normal waist circumference in Asians (5 options)
The main mechanisms underlying the physiopathology of NAFLD (4 options)
3. Knowledge of Diagnostics Domain:
Which one of these non-invasive methods do you use to diagnose NAFLD? (6 options)
How do you make the diagnosis of NASH related cirrhosis in the absence of liver biopsy? (4 options)
4. Knowledge of Intervention and Management Domain:
Initial option to treat patients with NAFLD (4 options)
Do you use pharmacotherapy only in patients with NASH? (2 options)

Conclusion: Despite growing burden of NAFLD, there is a significant knowledge gap. Better implementation of NAFLD guidelines and conferences by different societies may improve this gap.

NAFLD: Therapy

FRI082

A randomized, double blind, placebo-controlled trial of htd1801 (berberine ursodeoxycholate, budc) in patients with hypercholesterolemia: implications for its use in non-alcoholic steatohepatitis (NASH)

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Background and Aims: NASH is often associated with hyperlipidemia and diabetes. BUDC is an ionic salt of berberine (BBR, a plant-extracted compound with anti-oxidant and anti-microbial properties, commonly used for diabetes and heart disease) and UDCA (a secondary bile acid used in cholestatic liver disease which lowers serum aminotransferases in a variety of liver diseases, including NASH. We assessed pharmacokinetics, safety and tolerability of ascending doses of HTD1801 in overweight/obese patients with hypercholesterolemia and measured its effects on serum lipids, HbA1C and aminotransferases.

Method: We enrolled pts with serum LDL >2.59 mmol/L and BMI between 25 and 40 kg/m^2. Pts were excluded if they had recently been on lipid lowering agents, had a history of cardiac disease or severe, uncontrolled diabetes. Pts were randomized to receive ascending doses of HTD 1801 in 3 sequential groups: Group I. 500 mg/day of HTD1801 or matching placebo in a ratio of 3:1. Group II. 1,000 mg/day of HTD1801 or placebo, 3:1. Group III. 2,000 mg/day HTD1801 or placebo, 3:1. Study medication or placebo were given in 2 equal doses daily for 28 days. Disease markers were measured at baseline and day 28. Serum levels of BBR and UDCA were measured after single and multiple doses for PK profile of HTD1801.

Results: 50 subjects were enrolled, including 30 females, equally distributed across the 3 dosing groups, 38 receiving HTD1801 and 12 placebo. Only 2 had a history of diabetes. Half life of BBR in serum was about 8–10 hrs and for UDCA approximately 7 hrs. After repeated

dosing, accumulation was about 4x in BBR and 2x in UDCA. Serum lipids decreased in a dose-dependent fashion (see Table). HbA1C and ALT levels did not decrease significantly. The frequency of treatment-related adverse events was similar with placebo (66%) and active drug (67%), the most frequent complaint in both groups being headache; no study drug-related were reported.

	500 mg (n = 12)		1000 mg (n = 12)		2000 mg (n = 14)		Placebo (n = 12)	
Mean (μmol/L)	Baseline	28d	Baseline	28d	Baseline	28d	Baseline	28d
Total Cholesterol	6.13	5.88	5.81	5.54	5.91	5.42*	6.23	6.59
LDL	4.01	3.72	3.68	3.51	3.85	3.44**	3.91	3.85
Non-HDL cholesterol	4.85	4.71	4.48	4.31	4.62	4.14***	4.66	5.18
Triglycerides	2.11	2.27	1.76	1.86	1.60	1.54*	1.91	2.58

*p < 01; **p = 08; ***p < 0002.

Conclusion: HTD1801 was well tolerated for 28 days. Serum half life for both BBR and UDCA supported twice daily dosing. Dose-dependent lowering of serum lipid levels was observed, statistically significant for the highest dose group. A Phase 2 study of HTD1801 is currently underway in NASH.

FRI083

Weight loss and change in alanine aminotransferase (ALT) among patients with non-alcoholic fatty liver disease (NAFLD) receiving standard care in real world clinical practice: TARGET-NASH

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Background and Aims: Weight loss of 7% has been associated with improvement in liver histology among patients with non-alcoholic fatty liver disease (NAFLD). We estimated the association between weight loss and change in ALT among patients enrolled in TARGET-NASH.

Method: Patients enrolled in TARGET NASH between August 2016 and October 2019 with two or more weight measurements and an elevated ALT level (>30 U/L for males and >19 U/L for females) at the first weight measurement were included in the analysis. Patients with decompensated cirrhosis, bariatric surgery, weight loss medication, or a cancer diagnosis were excluded. Weight loss was defined as the difference between the baseline weight and the lowest measured weight over the follow-up study period. Weight loss was then categorized into ≥ 7% or <7% loss. Mean change in ALT was determined by using ALT values closest to the baseline and follow-up weights (within 3 months). The average change in ALT and the 95% CI were estimated among patients with an a priori goal weight change ≥ 7% and <7% using linear regression. Age at enrollment, race, gender, follow up time, insurance status, and body mass index (BMI) were thought a priori to be associated with weight loss and ALT and controlled for in the model.

Results: The study population included 1,006 patients. At enrollment, the median age was 56 years, 58% female, 70% white, 29% overweight, 31% obese class I and 33% obese class ≥ II, 13% had cirrhosis, and 37% had a history of diabetes. During a median follow up of 18.4 months, 24% of patients lost ≥ 7% weight, 57% of patients remained within 7% of baseline weight, and 19% patients gained >7% weight. Mean ALT level decreased by −24.05 IU/L (95% CI:−42.75, −5.42) among patients with ≥ 7% loss compared to patients whose weight loss was <7%.

Table: Estimated mean change in ALT by patient characteristics among patients who had a maximum weight loss ≥ 7% compared to patients who lost <7%*,#

Parameter	Estimate	Standard Error
Weight Loss ≥ 7% vs <7%	−24.08	9.52
Age at enrollment: ≥ 56 vs <56	16.56	6.20
Race: White vs Non-White	−8.10	6.80
Gender: Female vs Male	11.56	5.93
Months of Follow Up	0.43	0.23
Insurance Status at enrollment		
Private	−18.19	18.54
Medicare	−18.42	19.34
Medicaid	−20.96	19.62
Other	reference	reference
BMI category at baseline weight		
Underweight	17.17	65.72
Lean	−21.54	16.50
Overweight	−14.21	9.68
Obesity Class 1	−18.88	9.77
Obesity Class 2 and 3	reference	reference

*Interaction terms between BMI and weight change not shown.
#Estimates are adjusted for other patient characteristics shown in the table.

Conclusion: Weight loss of ≥ 7% may clinically improve ALT levels among patients with NAFLD receiving care in standard practice. These findings support results from randomized trials suggesting improvement in ALT among patients with NAFLD who participated in weight loss interventions.

FRI084

Gw9662, a peroxisome proliferator-activated receptor gamma antagonist, attenuates the development of non-alcoholic fatty liver disease

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is by now one of the most common liver disease worldwide. Besides a genetic predisposition, overweight and insulin resistance are among the main risk factors in the development of NAFLD. Peroxisome proliferator-activated receptor gamma (PPARγ), which belongs to a class of nuclear receptors, plays a pivotal role in the regulation of the expression of genes involved in lipid and glucose metabolism. Several studies suggest that hepatic expression of PPARγ is induced in NAFLD patients and experimental models while intervention studies suggest that targeting PPARγ activity with specific agonists may be beneficial. However, it has been reported that the PPARγ antagonist GW9662 may improve insulin sensitivity in settings of type 2 diabetes. Here, we determined the effects of a treatment with this antagonist of PPARγ on the development of NAFLD and molecular mechanisms involved.

Method: Female C57BL/6J mice were pair-fed either a liquid control diet (C) or a fat-, fructose- and cholesterol-rich (FFC) diet for 8 weeks. In addition, mice were treated with the PPARγ antagonist GW9662 (1 mg/kg body weight) i.p. 3 times per week. Indices of liver damage and inflammation, parameters of glucose metabolism and portal endotoxin levels were determined.

Results: Despite similar caloric intake and weight gain, mice fed a FFC diet showed marked signs of steatosis with beginning inflammation and elevated liver transaminase activity in plasma. Indices of liver damage including macrovesicular fat accumulation and numbers of inflammatory foci were significantly lower in FFC-fed mice concomitantly treated with GW9662 compared to FFC-fed mice. Alanine transaminase activity and area under the curve of glucose tolerance test were both significantly lower in FFC-fed mice treated with GW9662 when compared to FFC-fed mice. Furthermore, bacterial

endotoxin levels in portal plasma were higher in both FFC-fed groups than in controls, respectively, while concentrations were similar between FFC- and FFC+PPARγ-treated mice.
Conclusion: In summary, our data suggest that a treatment with the PPARγ antagonist attenuates the development of a diet-induced NAFLD and that this is not associated with changes of intestinal barrier function (DFG FKZ: BE2376/6-3).

FRI085
Obesity management during the rise of NAFLD: real world outcomes of the medical weight loss approach using a very low energy diet
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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is a rapidly growing cause of liver disease, with approximately a quarter of the global population now thought to be affected. It is more common in overweight and obesity, and at present loss of weight is the key treatment for NAFLD. Weight loss improves steatosis, and a loss of ≥ 10% of total body weight (TBW) can result in fibrosis regression. Despite this, weight loss is difficult to achieve and maintain, resulting in the need for effective, real world medical weight loss strategies. Medical weight loss often includes; Very Low Energy Diets (VLED), which induce ketosis to suppresses appetite, alongside the use of Appetite Suppressing (AS) medications. Here we aim to review the real world outcomes of a medical weight management clinic, which utilises this approach.
Method: We performed a single centre retrospective analysis of an outpatient weight management clinic at a tertiary referral centre between July 2015 and February 2019. All patients were offered a ketogenic VLED in order to achieve their target weight, with AS medications used to assist with weight loss or weight maintenance as required. The primary outcome was weight loss achieved at 3 and 6 months.
Results: 411 patients attended the clinic during this period, with the majority (92%) of patients commenced on the VLED. The median loss of weight was 8.2 kg (2.8–12.9) or 6.7% (2.4–10.9) of baseline TBW at 3 months (n = 227), and 11.8 kg (4.4–19.8) or 9.37% (3–15.8) of TBW at 6 months (n = 153). At 3 months 30% of the cohort were able to achieve ≥ 10% loss of TBW, which increased to 48% at 6 months. 35% of patients were also prescribed AS medications, with Topiramate the most commonly prescribed, followed by phentermine, then GLP-1 agonists. Those treated with pharmacotherapy more likely to achieve ≥ 10% loss of TBW at both 3 (30% vs 21%, p = 0.006) and 6 months (57% vs 34%, p = 0.005). There was some loss to follow up within the cohort, however patients who were more likely to remain in the clinic had previously tried pharmacotherapy (OR 0.57, 95%CI 0.3–0.96, p = 0.04), or other dietary methods of weight loss in the past (OR 0.44, 95%CI 0.3–0.7, p = 0.00).

Baseline cohort characteristics

	Overall	Female	Male	P-value
N	411	275 (67%)	136 (33%)	<0.0001
Age	47 ± 12	45 ± 12	50 ± 11	0.0001
Weight (kg)	129.8 ± 29	122.9 ± 25	144.2 ± 30	<0.0001
BMI (kg/m^2)	46.5 ± 8	46.7 ± 9	46.1 ± 7.7	0.5057
Waist circumference (cm)	129.6 ± 17	124.5 ± 16	140.5 ± 16	<0.0001
Waist Hip Ratio	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.1	<0.0001

Conclusion: An outpatient based ketogenic VLED program is an effective method of achieving weight loss, particularly in combination with pharmacotherapy. This is an effective real world approach to weight loss which should be considered in the management of obese patients with NAFLD.

FRI086
Supplementing diet with olive oil does not prevent the progression of non-alcoholic fatty liver disease
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Background and Aims: Besides general overnutrition the intake of certain macronutrients like fructose as well as the type of dietary fat intake and fatty acid composition seems to be of importance during development of non-alcoholic fatty liver disease (NAFLD). Indeed, it has been recommended that patients with NAFLD should follow a 'Mediterranean diet' being rich in vegetables, fruits but also olive oil. Findings regarding the addition of olive oil to the diet in settings of NAFLD and insulin resistance are still contradictory. Here, we evaluate the effect of exchanging dietary fat source from butterfat to olive oil on progression of an already existing diet-induced NAFLD in mouse model.
Method: Female C57Bl/6 mice were either fed a liquid fat-, fructose and cholesterol-rich diet (FFC, 25 E% from butterfat) or control diet (C) for 8 weeks. Some FFC- and C-fed mice were then switched on FFC- or C-diets containing olive oil for 5 more weeks (FFC+OO, 25 E% from olive oil, C+OO, 12 E% from OO), while other groups continuously received butterfat-containing diets (C, FFC). FFC and FFC+OO, as well as C and C+OO-fed mice were pairfed. One week prior to the end of the trial, glucose tolerance test (GTT) was performed and markers of liver damage and glucose metabolism were assessed at the end of the trial.
Results: After 8 weeks of feeding, FFC-fed mice had developed marked signs of NAFLD and insulin resistance which progressed after 13 weeks of feeding. Surprisingly, exchanging dietary fat source for last 5 weeks had no preventive effect on markers of liver damage. Indeed, NAFLD activity score and liver: to body weight ratio was similar between FFC and FFC+OO-fed mice. Furthermore, markers of lipid metabolism like sterol regulatory element-binding transcription factor-1c (Srebp1c) and fatty acid synthase (Fas) mRNA expression were also similarly induced in livers of FFC and FFC+OO-fed mice. Exchanging fat source in FFC diet also had no effect on the significantly higher fasting glucose levels as well as area under the curve during GTT. Also no differences regarding insulin receptor (Ir) or insulin receptor substrate-2 (Irs2) mRNA expression in muscle tissue were found between FFC-groups.
Conclusion: Taken together, our data suggest that exchanging butterfat with similar amounts of olive oil has no effect on the progression of diet-induced NAFLD as well as impairments of glucose metabolism in mice. (funded in parts by UFOP e.V.).

FRI088
Single doses of TERN-201, a novel selective semicarbazide-sensitive amine oxidase (SSAO) inhibitor, are safe, well-tolerated, and result in sustained reduction of SSAO activity in healthy participants
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Background and Aims: SSAO contributes to non-alcoholic steatohepatitis (NASH) by increasing oxidative stress through deamination of primary amines (e.g. methylamine, MMA) to aldehyde, ammonium, and H_2O_2 and by recruitment of inflammatory cells to the liver, exacerbating hepatic inflammation and injury. SSAO levels are

elevated in NASH and correlate with fibrosis stage. TERN-201 is a novel, selective, covalent SSAO inhibitor that decreases liver inflammation and fibrosis in a rat model of NASH. We conducted a single-ascending dose clinical trial of TERN-201 and report the first pharmacokinetic (PK) and pharmacodynamic (PD) target engagement data for an SSAO inhibitor in humans.

Method: Four groups of 8 healthy participants were randomized to receive TERN-201 capsule or matching placebo in a 3:1 ratio. Plasma levels of TERN-201 and PD biomarkers were determined at pre-dose and various timepoints post-dose. SSAO inhibition was determined by measuring relative reductions in plasma H_2O_2 generation after addition of an exogenous substrate (benzylamine). Endogenous methylamine (MMA) levels, predicted to increase upon SSAO inhibition, were measured in plasma. Safety was assessed for 7 (±3) days after dosing.

Results: 32 healthy human participants (100% male, 63% Black, 19% Asian, 13% Caucasian) were enrolled and received a single oral dose of TERN-201 (1, 3, 6, and 10 mg, n = 6 each) or placebo (n = 2). TERN-201 plasma PK exposure increased in a greater than dose proportional manner between the 3 and 10 mg dose levels. The mean half-life of TERN-201 ranged from 1–3 hours. At 4 hours post-dose, near complete inhibition of plasma SSAO activity was seen in all dose cohorts and continued suppression was detected for up to 1 week after a single dose of TERN-201. Maximum plasma MMA levels increased with TERN-201 dose. No clinically relevant adverse events or laboratory abnormalities were reported.

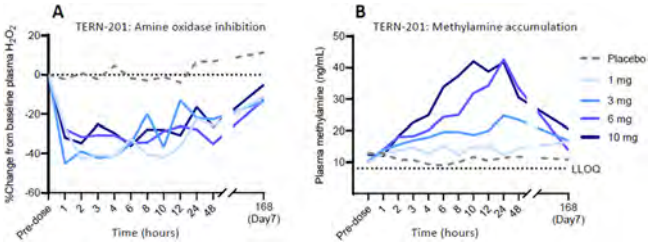

Figure Inhibition of total amine oxidase levels (A) and accumulation of methylamine (B) in the plasma of healthy participants receiving a single dose of TERN-201 or placebo.

Conclusion: Inhibition of plasma SSAO amine oxidase activity and dose-dependent increases in plasma MMA were sustained up to 1 week after single doses of TERN-201, suggesting potent, covalent target engagement and supporting once daily dosing despite a short plasma half-life. All TERN-201 dose levels were well-tolerated. Additional studies are warranted to further investigate TERN-201 for the treatment of NASH.

FRI089

Decline in NASH and atherosclerosis-associated oxidised phospholipids and 7-ketocholesterol in response to icosabutate therapy

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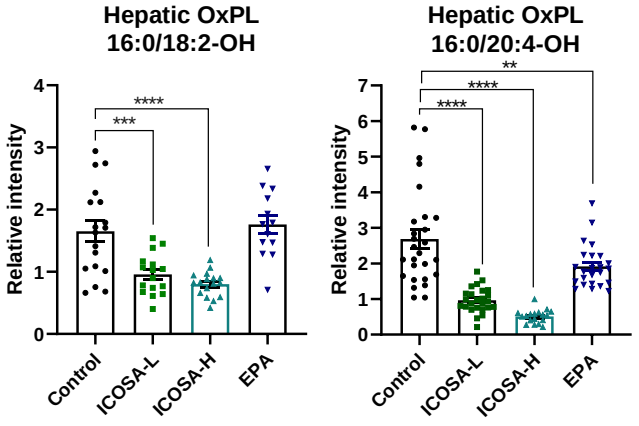
Background and Aims: Oxidative stress plays a central role in the pathology of both non-alcoholic steatohepatitis (NASH) and atherosclerosis. We have recently shown that icosabutate, a structurally engineered omega-3 fatty-acid (EPA) derivative resistant to β-oxidation and membrane incorporation, significantly reduces markers of hepatic oxidative stress (oxidised glutathione) in multiple murine NASH models and systemic oxidative stress (plasma gamma-glutamyltransferase) in hyperlipidemic humans. To investigate if these findings extend to pathology-associated oxidised lipids, we assessed hepatic concentrations of oxidised phospholipids (oxPLs) in mice and plasma concentrations of 7-ketocholesterol (7-KC) in humans treated with icosabutate.

Method: 9-week old C56BL/6J mice were fed a moderately high-fat diet (31% fat) for 6 weeks, then continued with the diet but received treatment with either low (56 mg/kg, ICOSA-L) or high (112 mg/kg, ICOSA-H) dose icosabutate or EPA (equimolar to ICOSA-H) for 6 weeks (9 mice per group). Changes in hepatic concentrations of oxPLs (16:0/18:2-OH and 16:0/20:4-OH isomers) were measured and differences versus baseline assessed via ANOVA with Dunnet's correction. In hyperlipidemic subjects (n = 15) temporarily withdrawn from statins (NCT02364635), plasma concentrations of 7-KC were assessed at day 0 (baseline), 7 and 28 (study end) in response to either 600 mg/d icosabutate (n = 15) or placebo (n = 5) and differences versus both baseline and placebo were assessed via ANOVA as a univariate procedure.

Results: Icosabutate, but not EPA, reduced hepatic 16:0/18:2 oxPL concentrations (−43%, $p < 0.01$ and.
−53%, $p < 0.001$ for low- and high-dose respectively). Both icosabutate and EPA reduced hepatic 16:0/20:4 oxPL concentrations, with the most pronounced decrease occurring in response to icosabutate (−57% and −71% for low- and high-dose respectively, both $p < 0.001$) versus −18% for EPA, ($p < 0.01$). In humans, icosabutate markedly reduced plasma concentrations of 7-KC by −54% at day 7 ($p < 0.01$) and −42% at day 28 ($p < 0.05$) versus baseline and −37% at day 7 and −39% at day 28 versus placebo (both $p < 0.01$). The reductions in 7-KC exceeded the −23% (day 7) and −35% (day 28) reductions in LDL-C versus baseline (both $p < 0.01$).



Conclusion: Icosabutate effectively reduces pro-inflammatory oxidised lipids in both liver and plasma. Marked decreases in hepatic oxPLs were observed in mice despite icosabutate's resistance to membrane incorporation whilst decreases in plasma 7-KC exceeded the decreases in plasma LDL-C in humans. These findings support the therapeutic potential of icosabutate for the treatment of both NASH and atherosclerosis via a reduction in pathology-associated oxidised lipids.

FRI090

Aramchol improves glucose and lipid homeostasis in NASH via regulation of AMPK and mTOR

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Background and Aims: Arachidyl amido cholanoic acid (Aramchol) is a potent downregulator of hepatic SCD1 protein expression that reduces liver triglycerides (TG) and fibrosis in animal models of steatohepatitis. In a phase IIb clinical trial, Aramchol improved the histological features of non-alcoholic steatohepatitis (NASH) and reduced blood levels of hemoglobin A1c (HbA1c). We aimed at assessing lipid and glucose metabolism in mouse hepatocytes and in a mouse model of NASH (0.1MCD, 0.1% methionine and choline deficient diet) after treatment with Aramchol.
Method: Mouse hepatocytes were incubated with 20 μM Aramchol for 48 hours. C57BL/6 mice fed a control diet or 0.1MCD diet for 4 weeks received Aramchol (1 or 5 mg/kg/day) or vehicle by gavage for the last 2 weeks.
Results: Proteomics and Western blot analysis showed that the activity of AMP activated protein kinase (AMPK) was increased while the activity of nutrient sensor mammalian target of rapamycin complex 1 (mTORC1) was decreased by Aramchol in hepatocytes. This translated into changes in the content of their downstream targets including proteins involved in fatty acid (FA) synthesis and oxidation (SCD1, P-ACCα/β(S79), CPT1a/b, HADHA and HADHB), oxidative phosphorylation (NDUFA9, NDUFB11, NDUFS1, NDUFV1, ETFDH and UQCRC2), tricarboxylic acid (TCA) cycle (MDH2, SUCLA2 and SUCLG2), P-p70S6K(T389), and P-S6(S235/S236). The protein content of HMGCR and FDPS, two rate-limiting steps in the synthesis of cholesterol was unchanged. Flux experiments with ^{13}C-uniformely labeled glucose showed that TCA cycle cataplerosis was reduced by Aramchol in hepatocytes. Finally, liver metabolic analysis showed that glucose homeostasis is improved by Aramchol in 0.1MCD fed mice in a dose-dependent manner.
Conclusion: Our study shows that hepatocytes respond to Aramchol treatment by activating AMPK and inhibiting mTORC1, which in turn activate FA β-oxidation and oxidative phosphorylation inhibiting de novo lipogenesis, gluconeogenesis and cataplerosis. These results offer a possible explanation for downregulation of HbA1c as well as for the reduction in hepatic TG observed in NASH patients treated with Aramchol.

FRI091
Saroglitazar for the treatment of NAFLD patients: a single- center observational study at 52 weeks follow up

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Background and Aims: Saroglitazar a dual PPAR alpha and PPAR gamma agonist is approved for management of Diabetic Dyslipidemia and Hypertriglyceridemia in India. Considering the association between insulin resistance, dyslipidemia and the development of NAFLD/NASH, Saroglitazar could potentially benefit patients with NAFLD including those with borderline NASH. Therefore, the purpose of the present study was to examine the efficacy of saroglitazar in patients with NAFLD.
Method: This study was Single Center, Single arm, Prospective Observational study conducted in Southern India. A total of 52 patients Diabetic and Non-Diabetic diagnosed as fatty liver on USG and with Liver Stiffness Measurement (LSM) >6 kPa were prescribed Saroglitazar 4 mg once daily. The Males (71.15%) and Females (28.84%) with Mean age of 45.8 ± 11.6 years and Mean Body Mass Index 28.1 ± 6.0 Kg/m^2 were followed up for the period of 52 weeks for body weight, ALT (Alanine Aminotransferase), AST (Aspartate Aminotransferase), Serum triglycerides and LSM. Statistical analysis was done using Paired sample student t -test.
Results: In this study 28.8% were Diabetic and 17.3% were hypertensive. Patients were Normal (21.15%), Overweight (11.54%), Obese I (32.69%) and Obese II (34.62%) as per WHO Asian criteria based on BMI. Saroglitazar treatment was associated with significant reduction in ALT (56.1 ± 30.9 to 33.5 ± 16.7IU/L) and AST (46.7 ± 22.3 to 29.4 ± 11.1 IU/L), Serum triglycerides reduced significantly from (193 ± 56.75 mg/dL to 133.11 ± 37.04 mg/dL) and Liver Stiffness Measurement at baseline 12.3 ± 9.9 kPa was significantly reduced to 9.6 ± 4.5 kPa at 52 weeks follow up. Percentage reduction in the above parameters are summarized in Table 1. There was slight variation in weight (75.2 ± 13.8 to 73.9 ± 13.5 kg). Overall, Saroglitazar was well tolerated during the study.

Table 1: Change in efficacy endpoints from baseline to week 52.

Parameters	Percentage Reduction	P Value at 95% CI
ALT	40.3%	<0.001
AST	36.9%	<0.001
Serum Triglycerides	31.0%	<0.001
Liver Stiffness Measurement	21.0%	0.02
Body Weight	1.7%	0.005

Conclusion: Saroglitazar 4 mg once daily improved the liver enzymes, serum triglycerides and Liver Stiffness measurement. Further studies are needed to substantiate the efficacy and safety of Saroglitazar.

FRI092
The pharmacokinetics, pharmacodynamics, and short-term safety of cilofexor, a nonsteroidal farnesoid X receptor agonist, in subjects with hepatic impairment

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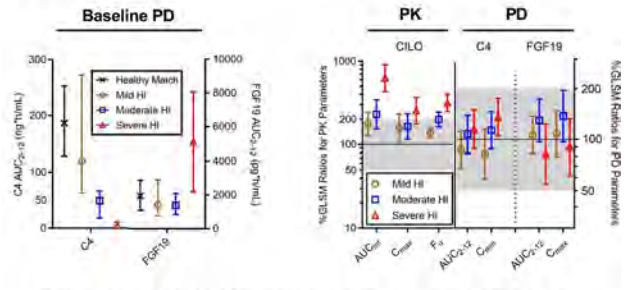
Background and Aims: Cilofexor (CILO) is a selective, oral, nonsteroidal farnesoid X receptor (FXR) agonist in development for the treatment of nonalcoholic steatohepatitis (NASH) and primary sclerosing cholangitis (PSC). This Phase 1 study evaluated the short-term safety, pharmacokinetics (PK), and pharmacodynamics (PD) of CILO in subjects with mild, moderate, or severe hepatic impairment (HI) to support development of CILO in patients with cirrhosis.
Method: Subjects with stable mild, moderate, or severe HI (Child-Turcotte-Pugh [CTP] A, B, or C, respectively, [n = 10/group]) and healthy matched controls with normal hepatic function (by sex, age, and BMI) underwent intensive PD sampling on Day-1 and received a single, oral dose of CILO (30 mg CTP-A, -B; 10 mg CTP-C) on Day 1 with intensive sampling for PK (96 hr) and PD (24 hr). Safety was monitored and the effect of HI on PK parameters (AUC, Cmax, free fraction [f_u]) of CILO and its major circulating metabolites (GS-716070 and GS-156765), as well as PD parameters (C4 and FGF19), were evaluated. Geometric least square mean ratios (GLSM ratios) and 90% confidence intervals (CIs) relative to controls are reported.
Results: Treatment-emergent adverse events (AEs) were generally mild. Two subjects (with moderate and severe HI), both with histories of esophageal varices, experienced serious AEs of GI hemorrhage, considered unrelated to study drug. Preliminary data summarizing the effect of varying degrees of HI on PK and baseline-corrected PD are presented in the Figure. Systemic/free exposures of CILO and its major circulating metabolite GS-716070 were increased, whereas GS-1056756 exposure was decreased with increasing severity of HI. Whereas PD response to CILO was similar in subjects with mild or moderate HI compared to controls, subjects with severe HI had reduced response, likely due to baseline activation of the FXR pathway (Figure).

Figure 1 Effect of HI on the PD, and PK/PD of CILO



C4, 7α-hydroxy-4-cholesten-3-one; FGF19, fibroblast growth factor 19; GLSM ratio, geometric least square mean ratio (HI/healthy matched control); AUC, area under the curve; Cmax, maximum plasma concentration; F_u, free fraction; grey shaded area represents the 50% - 200% boundary

Conclusion: CILO was generally well tolerated in this study. The moderate (<2-fold) changes in CILO PK in subjects with mild HI is unlikely to be clinically relevant and support administration without dose modification in this population. Reduced PD response in severe HI is likely related to baseline activation of the FXR pathway.

FRI093

Concentration-QT analysis of firsocostat, a liver-targeted acetyl-coa carboxylase inhibitor

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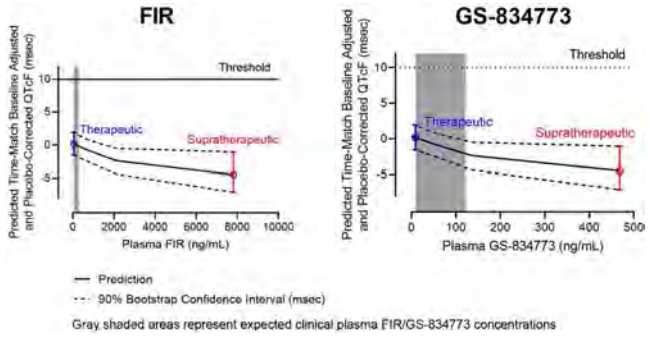
Background and Aims: Patients with nonalcoholic steatohepatitis (NASH) have an increased risk of cardiovascular disease. Firsocostat (FIR) is a potent, oral, liver-targeted inhibitor of acetyl-CoA carboxylase (ACC) in development for the treatment of NASH. In animals, no electrocardiographic (ECG) abnormalities have been observed at a dose providing a >300-fold exposure margin relative to the human clinical dose (20 mg daily). In this first-in-human, placebo-controlled, single ascending dose study, intensive ECG monitoring was conducted to evaluate the potential pro-arrhythmic risk of FIR.
Method: High quality, intensive, time-matched 12-lead ECGs were obtained from healthy subjects administered single doses of FIR up to 1000 mg. Effects of FIR, GS-834773 (primary metabolite of FIR produced by UDP-glucuronosyltransferases (UGTs)), and their interaction on baseline-adjusted Friedrich's correction QT(ΔQTcF) were modelled using linear mixed-effects models. Bootstrapping was used to obtain 90% confidence intervals (CIs) of predicted placebo-corrected ΔQTcF (ΔΔQTcF) to evaluate the potential risk of QT prolongation.
Results: C_{max} at FIR 1000 mg provided a supratherapeutic concentration that was at least 3-fold higher than the maximal expected concentrations of FIR and GS-834773 in subjects with moderate hepatic impairment co-administered UGT inhibitors. Figure 1 shows the relationships between ΔΔQTcF and concentrations of FIR and GS-834773. The upper bounds of the 90% CIs for predicted ΔΔQTcF were <10 msec, indicating the absence of QT prolongation at therapeutic and supratherapeutic concentrations of FIR and GS-834773.



Gray shaded areas represent expected clinical plasma FIR/GS-834773 concentrations

Figure: Association between predicted ΔΔQTcF and plasma FIR/GS-834773 concentrations

Conclusion: This concentration-QT study showed that FIR does not cause QT prolongation at the highest exposures expected in the clinical setting. These data formed the basis of a waiver that obviated the requirement for a thorough QT (TQT) study by the US FDA. The cardiovascular safety of FIR will be confirmed in ongoing and future studies of patients with NASH.

FRI094

The safety and pharmacokinetics of fenofibrate in patients with advanced fibrosis including those with non-alcoholic steatohepatitis (NASH)

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Background and Aims: Fenofibrate (FENO), a lipid-lowering PPAR-α agonist, is contraindicated in patients with advanced hepatic fibrosis due to lack of prior studies. FENO has shown promise for mitigating hypertriglyceridemia observed in NASH patients treated with the acetyl-CoA carboxylase (ACC) inhibitor firsocostat (FIR). Here, we describe Ph 1 and 2 studies that evaluated the pharmacokinetics (PK) and safety of FENO in patients with advanced fibrosis to support coadministration with FIR.
Method: In the Ph 1 study, subjects with mild hepatic impairment (HI) (Child-Turcotte-Pugh [CTP]-A) and healthy matched controls (n = 10/group) received a single, oral dose of FENO 48 mg with intensive PK sampling. In the Ph 2 study, 31 patients with hypertriglyceridemia (TGs >150 and <500 mg/dL) and advanced fibrosis (F3-F4) due to NASH were randomized (1:1) to treatment with FENO 48 mg (n = 15) or 145 mg (n = 16) orally once daily for 2 weeks, followed by the combination of FENO+FIR 20 mg daily for 24 weeks (NCT02781584); an optional PK substudy was included (n = 16). Safety was monitored throughout both studies. Plasma concentrations of fenofibric acid (the active moiety of fenofibrate) were determined by validated LC-MS/MS methods. Geometric least squares mean ratios (GLSMRs) and 90% confidence intervals (CIs) of FENO AUC and C_{max} were constructed for subjects with mild HI vs healthy matched controls. PK parameters in NASH patients were dose-normalized for comparison.
Results: In the Ph 1 HI study, no treatment-emergent adverse events (TEAEs) or ≥ Grade 3 laboratory abnormalities were reported in patients with CTP-A cirrhosis. In NASH patients with F3-F4 fibrosis, there was no evidence of hepatotoxicity, or difference in frequency of TEAEs (no Grade 3–4) or laboratory abnormalities between dose groups. No clinically meaningful differences in fenofibric acid AUC_{inf} (GLSMR 1.25 [90% CI 89, 174]) or C_{max} (GLSMR 1.09 [90% CI 81, 146]) were observed between subjects with mild HI and healthy matched controls. In patients with NASH, dose-normalized fenofibric acid exposures were similar between those with F3 (n = 12) and F4 (n = 4) fibrosis and similar to mild HI.
Conclusion: In patients with mild HI or NASH with advanced fibrosis, FENO was well tolerated and the PK of fenofibric acid was unaltered. These data suggest that FENO may be a safe option for the management of hypertriglyceridemia in patients with advanced fibrosis and represent a meaningful contribution to our understanding of the PK of FENO in a previously unevaluated population.

FRI096

A randomized, double-blind, placebo-controlled, first-in-human single ascending dose, multiple ascending dose, and food effect study to evaluate the safety, tolerability, and pharmacokinetic profile of FM101 in healthy volunteers

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Background and Aims: FM101 is a highly potent modulator of human A_3 adenosine receptor (A_3AR) over-expressed in inflammatory cells. We have previously shown anti-inflammatory and -fibrotic activities of FM101 in non-alcoholic steatohepatitis (NASH) animal models including the Stelic animal model (STAM) and Fast Food Diet (FFD). To explore the potentiality of FM101 as a therapeutic, this first-in-human (FIH) study was performed by evaluating the safety, tolerability, and pharmacokinetic (PK) profile of FM101 in healthy subjects.

Method: This was a randomized, double-blind, placebo-controlled, first-in-human (FIH) study consisting of three parts: a single ascending dose (SAD) part, a single dose of food effect (FE) part, and a multiple ascending dose (MAD) part. The primary objectives of the study were to evaluate the safety/tolerability and the pharmacokinetics (PK) of FM101 after single and multiple oral dose administration to healthy volunteers. The secondary objective was to evaluated the food effect on the single dose PK of FM101 in healthy volunteers. As exploratory, we investigated the PKs of FM101 and its major metabolite M6 in the urine after MAD administration. Fifty subjects were entered onto this study. A single dose of FM101 was escalated from 75 mg to 2400 mg per patient in SAD study. A single dose of 300 mg was administered in FE study. A multiple dose of FM101 for a period of one week was escalated from 150 mg QD to 450 mg QD and 600 mg BID, respectively.

Results: No clinically relevant safety and tolerability findings were observed in all safety variables such as laboratory values, vital signs, or electrocardiograms. All adverse events (AEs) reported during the study were mild of intensity and local toxicities in the gastrointestinal tract were most frequently observed in the forms of nausea and diarrhea. The FM101 was rapidly absorbed and plasma concentrations declined with a mean terminal half-life of approximately 18 h.

Table 1. Summary of Related TEAEs by Treatment, SOC and PT

System Organ Class Preferred Term [1]	Placebo (N=6) E n (%)	150 mg QD (N=6) E n (%)	450 mg QD (N=6) E n (%)	600 mg BID + 600 mg SD (N=6) E n (%)	Total Active (N=18) E n (%)	Total (N=24) E n (%)
Any Adverse Events		1 1 (16.7)	9 6 (100)		10 7 (38.9)	10 7 (29.2)
Gastrointestinal disorders			8 6 (100)		8 6 (33.3)	8 6 (25.0)
Nausea			7 6 (100)		7 6 (33.3)	7 6 (25.0)
Diarrhoea			1 1 (16.7)		1 1 (5.6)	1 1 (4.2)
General disorders and administration site conditions			1 1 (16.7)		1 1 (5.6)	1 1 (4.2)
Fatigue			1 1 (16.7)		1 1 (5.6)	1 1 (4.2)
Nervous system disorders		1 1 (16.7)			1 1 (5.6)	1 1 (4.2)
Headache		1 1 (16.7)			1 1 (5.6)	1 1 (4.2)

Figure: (abstract: FRI096)

Table 2. PK parameters in MAD cohort 2 (450 mg)

Subject Number/ Statistic	Cmax (ng/mL)	Tmax (h)	AUC0-24h (ng.h/mL)	CL/F (L/h)	Vz/F (L)	Acc. Ratio AUC0-24h	t1/2 (h)	Kel (/h)
309	1140	1.00	4559	98.7	2402	1.05	16.9	0.0411
310	1170	2.00	3477	129	3313	1.23	17.7	0.0391
312	1230	1.03	4329	104	1064	0.93	7.09	0.0977
314	1400	4.00	9102	49.4	2119	2.25	29.7	0.0233
315	1700	1.00	4972	90.5	2085	0.99	16.0	0.0434
316	931	2.00	6347	70.9	3195	1.31	31.2	0.0222
N	6	6	6	6	6	6	6	6
Mean	1262		5464	90.5	2363	1.29	19.8	0.0445
SD	263		2015	27.7	827	0.49	9.14	0.0276
CV (%)	20.8		36.9	30.6	35.0	38.1	46.2	62.2
Median	1200	1.52	4765	94.6	2260	1.14	17.3	0.0401
Min	931	1.00	3477	49.4	1064	0.93	7.09	0.0222
Max	1700	4.00	9102	129	3313	2.25	31.2	0.0977
Geometric mean	1240		5197	86.6	2219	1.23	17.8	0.0390

Figure: (abstract: FRI096)

Steady-state levels were achieved within a week. The FM101 area under the curve from time 0 to infinity and peak or maximum FM101 concentration seemed to increase with escalating dose, which suggests that FM101 has linear pharmacokinetics.
Conclusion: The prevalence of NASH gradually increases over time due to the epidemics of obesity and metabolic diseases including diabetes. There is no standard of care for this chronic type of disease so far. In this study, we demonstrated that FM101, a potential drug for treating NASH was generally well-tolerated up to 2400 mg (QD) and 600 mg (BID) in SAD and MAD studies, respectively. It also had a linear PK profile without significant inter-individual variations in healthy subjects. Based upon the obtained results, FM101 is considered as a suitable drug candidate for future evaluation in patients with inflammatory and fibrotic diseases including NASH.

FRI097

Direct access lifestyle training improves liver biochemistry and causes weight loss but uptake is suboptimal in patients with NAFLD

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Background and Aims: EASL NAFLD guidelines recommend a comprehensive and pragmatic individualised approach to lifestyle modification. Delivery of such interventions in busy clinics in the United Kingdom is challenging due to organisational pressures borne out in a recent survey where only 1 in 5 practices polled were able to offer adequate access to multidisciplinary weight management services.(1) Evidence on the acceptability, uptake and efficacy of direct access intensive lifestyle training program offered in secondary care where adequately provided is lacking. We aimed to assess the uptake of lifestyle training and its impact in patients with NAFLD.
Method: All patients attending a dedicated NAFLD clinic from April 2018 to March 2019 were offered referral to a lifestyle trainer program funded by Liverpool Council via a representative present in clinic. The program involves the patient seeing a health trainer in community hubs or GP practices close to the patient's home on a weekly or fortnightly basis for 12 weeks. Personalised advice and support is offered to complete objectives set out in a Personalised Health Plan based on Public Health England guidelines. We compared weight loss and changes in ALT between patients who completed the program versus age and sex matched patients who did not.
Results:167 patients with fatty liver disease were offered lifestyle training during the study period. Median age of patient was 58 yr; Only 16 (9.58%, 95% CI 6%–15%) patients completed the program. Weight loss in the intervention group was significantly higher compared to the control group (–2.79 Kg vs + 0.95 Kg, p = 0.007). A drop in ALT was noted in both groups though this was not statistically significant (–20.6 IU/L vs –15.75 IU/L p = 0.579). Completing the program was not associated with improvement in lipid profiles but was associated with an improvement in self rated emotional wellbeing (56.25% to 75%), an increase in fruit intake by 61.7%, reduction in the use of fried food and snacking by 13% and 21% respectively.
Conclusion: Dedicated direct access health trainer input resulted in significant weight loss but had no impact on liver biochemistry or lipid profile over 3 months. Only 1 in 10 patients offered the opportunity completed the program, reasons for which should be a focus for further research

Reference

1. Sheridan DA, et al. Care standards for NAFLD in the UK 2016: A cross-sectional survey. *Frontline Gastro*. 2017Oct1;8(4):252–9.

FRI098

Motile sperm domain-containing protein 2: a novel therapeutic target for the treatment of non-alcoholic steatohepatitis

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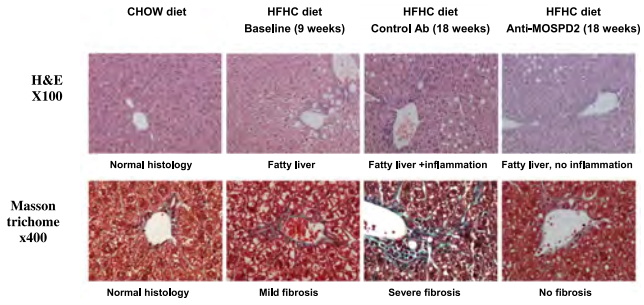
Background and Aims: Nonalcoholic fatty liver disease (NAFLD) is a major cause of liver-related morbidity and mortality worldwide with no effective treatment currently available. In the absence of circulating monocytes or treatment with Ceniciviroc, an oral CCR2/5 antagonist that inhibits monocyte migration, Nonalcoholic steatohepatitis (NASH) and liver fibrosis were shown to be reduced. These findings indicated that inhibiting monocyte migration could have a therapeutic benefit in NASH. We previously identified MOSPD2 (Motile sperm domain–containing protein 2) as a protein which is predominantly expressed on the surface of human monocytes and is essential for their migration. In this study, the potential of MOSPD2 as a target for treating NASH was assessed. The efficacy of anti-MOSPD2 monoclonal antibody (mAb) compared with Ceniciviroc to inhibit monocyte migration in-vitro was tested.
Method: MCP-1 and RANTES were used to induce migration of primary human monocytes through a trans-well plate. MOSPD2 knockout (KO) mice were generated by homologous recombination. Anti-MOSPD2 mAbs were prepared by immunizing mice with the extracellular region of human MOSPD2 and isolating hybridoma producing antibodies. NASH was induced in mice by using a High-Fat High-Carbohydrate (HFHC) diet.
Results: Anti-MOSPD2 mAb significantly inhibited MCP-1 and RANTES-induced migration of monocyte and was superior to Ceniciviroc in-vitro. In a NASH model induced by HFHC diet, MOSPD2 KO mice showed significant decrease in liver inflammation and fibrosis compared with wild type controls. Furthermore, employing anti-MOSPD2 mAb in the HFHC model after fibrosis was initiated halted and reversed the disease.



Conclusion: The results indicate that MOSPD2 is playing a role in NAFLD pathogenesis, and that targeting MOSPD2 using mAbs may hold promise as a treatment for NASH and liver fibrosis through inhibition of monocytes accumulation in the liver.

FRI099

The efficacy of vitamin D supplementation on NAFLD: a randomized, double-blind, placebo-controlled 12- month trial on 311 patients

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Background and Aims: Nonalcoholic fatty liver disease (NAFLD) is common cause of liver disease worldwide which can eventually cause chronic liver damage. Current studies suggest that vitamin D supplementation may have a favorable effect on the management of NAFLD. The aim of the present randomized controlled trial and was to evaluate potential impact of vitamin D supplementation on the transient elastography indices of liver steatosis (CAP) and fibrosis (LSM) as primary outcome and AST, ALT and GGT as secondary outcomes in adult patients with NAFLD.
Method: This randomized, double-blind, placebo-controlled 12-month trial was conducted at a single tertiary center in Rijeka, Croatia. Eligible patients were randomized (2:1) to vitamin D3 oral solution (1000 IU/day; 5 drops) or a matching placebo. Eligible for inclusion were adult patients with NAFLD on ultrasound and with at least one clinical marker of the metabolic syndrome. Excluded were patients with any other potential cause of liver steatosis/fibrosis. Patients were evaluated at baseline and after 6 and 12 months of treatment with transient elastography FibroScan® to assess CAP and LSM and blood analysis.
Results: A total of 311 pts were enrolled and randomized, 201 to vitamin D 1000 IU/day and 110 to placebo. There appeared a clear decreasing trend in CAP over time in vitamin D-treated patients and a slight increasing trend in the placebo arm (Figure 1). No such trends were apparent regarding LSM and liver enzymes. There was vitamin D – placebo difference in change vs. baseline of –22.1 dB/m (95% CI –32.2, –12.0) after 180 days and of –49.4 dB/m (95% CI –59.6, –39.3) after 360 days of treatment (95% CI adjusted for multiplicity). The treatment*visit interaction was significant ($P < 0.001$), i.e., between-treatment difference in change vs. baseline was greater after 360 days than after 180 days of treatment (difference in between-treatment difference = –27.4 dB/m, 95% CI –36.0, –18.7). The vitamin D - placebo difference in change vs. baseline was –0.89 kPa (95% CI –1.60, –0.17) after 180 days, and –0.72 kPa (95%CI –1.43, –0.00) after 360 days of treatment (95% CI adjusted for multiplicity).
Conclusion: Our study suggest the efficacy of vitamin D supplementation on CAP reduction, while this was not the case for LSM, AST, ALT and GGT. Since there are still no FDA approved drugs for NAFLD so far, vitamin D may be a good therapeutic option, esspetially due to the safety and favorable cost/benefit ratio.

FRI100

Molecular, cellular, and pharmacological characterization of beta-selective partial agonists of human thyroid hormone receptor for the treatment of non-alcoholic steatohepatitis

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Background and Aims: Thyroid hormone receptor (THR) agonists currently in clinical trials for the treatment of nonalcoholic steatohepatitis (NASH) have demonstrated potential to reduce liver fat and restore liver function. These beneficial effects are attributed to an intra-hepatic activation of the beta (B) receptor isoform. Activation of the alpha (A) isoform in the heart with non-selective THR agonists has previously been reported and is considered detrimental for NASH patients. The aim of our project is to characterize novel THR agonists with no activation potential against THR-A.
Method: Binding between small molecule agonists and THR-A or -B resulting in coactivator recruitment was assessed in a FRET-based biochemical assay. The primary cell-based assay relied on HEK293 T cells transiently transfected with a luciferase reporter and a THR-A or -B expression plasmid. Activation of THR in Huh-7 hepatic cells was measured by qPCR. Compounds with favorable in vivo pharmacokinetics were evaluated for efficacy in High Fat Diet (HFD) rats.
Results: We discovered a series of novel THR agonists that were evaluated in a panel of in vitro functional assays. In a biochemical assay, the compounds activated THR-B with an EC_{50} of around 40–60 nM, and a maximum effective amplitude (E_{max}) of ~25–50% compared to the natural thyroid hormone T3. The same compounds did not significantly activate THR-A at concentrations up to 10 µM. In a HEK293T-based reporter assay, we observed a similar behavior of E_{max} value at ~55% compared to T3, with no measurable activation of the A-receptor, resulting in a selectivity index of more than 90-fold. The selective partial agonism effect on THR-B was confirmed for these compounds by measuring changes in gene expression in hepatocytes. These results are in contrast with all other known thyromimetic agents reported to date. In the cellular reporter assay, the B/A selectivity index of GC-1, MGL-3196 and VK-2809 (active form) ranged between 1- to 3.4-fold. In a HFD rat efficacy model, single doses of these highly B-selective THR partial agonists induced reduction in atherogenic lipids, but at lower levels compared with full agonists.

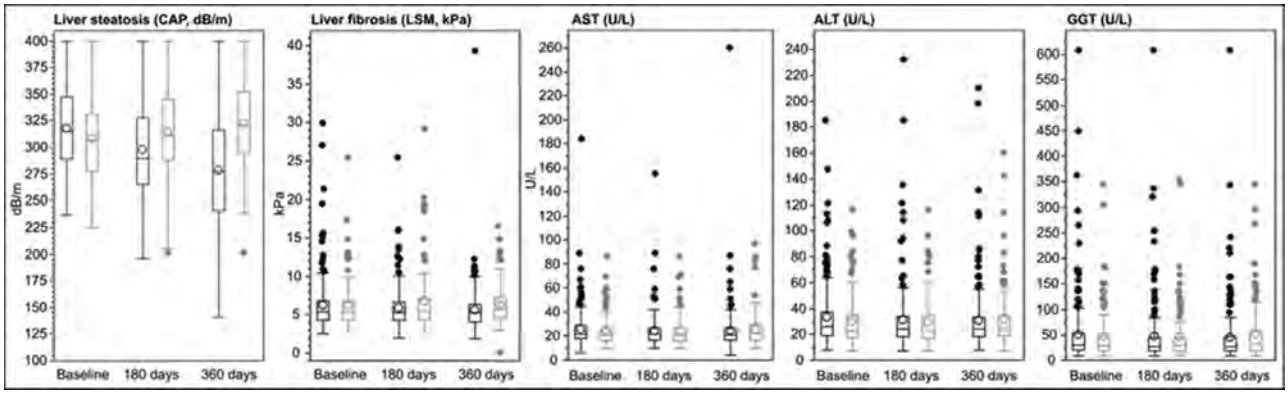
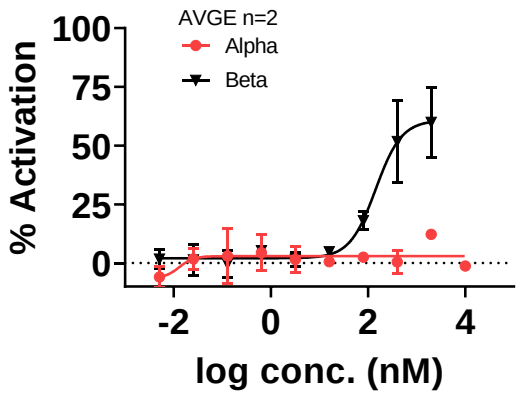


Figure 1: (abstract: FRI099): Primary and secondary outcomes of the study.



Conclusion: We discovered a novel series of B selective THR partial agonists. As described for other nuclear receptors, selective partial agonists of THR hold the promise of lowering liver fat with minimum risk of inducing the side effects described with non-selective full agonists.

FRI101

The first double-blind randomized placebo-controlled phase 2 study to assess the efficacy and safety of insulin sensitizer in patients with non-alcoholic steatohepatitis in Asia- an interim report

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Background and Aims: Non-alcoholic steatohepatitis (NASH) is the leading liver disease globally. Insulin sensitizer has been demonstrated the efficacy in lowering liver fat and inflammation of NASH patients. We conducted the randomized trial aiming to investigate the efficacy and safety of insulin sensitizer in Asian NASH patients.
Method: A total of 90 biopsy-proved NASH patients was consecutively randomized into receiving either oral Pioglitazone 40 mg/day or placebo for 24 weeks and another 12 weeks post-treatment follow up. Biochemistry profiles, liver biopsy and magnetic resonance imaging (MRI) were collected before and after the intervention, respectively. The histological severity of NASH was evaluated and the primary endpoint was the efficacy of pioglitazone in liver biochemistry and fat accumulation.
Results: Among the 90 NASH patients recruited, 66 (73.3%) were male and the mean age was 44.1 ± 12.7 years old. Diabetes, dyslipidemia, and metabolic syndrome were found in 21 (23.3%), 55 (61.1%), and 52 (57.8%) of the patients. The mean body mass index (BMI) was 28.9 ± 3.9 kg/m^2 and 29 (32.2%) patients of obesity. The mean AST, ALT, glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, and uric acid were 52 ± 23 U/L, 90 ± 39 U/L, 103.8 ± 16.2 mg/dl, 215.1 ± 33.7 mg/dl, 44.0 ± 10.6 mg/dL, 141.1 ± 35.2 mg/dL, 165.6 ± 116.0 mg/dL, and 6.8 ± 1.4 mg/dL, respectively. The mean HOMA-IR was 2.82 ± 2.74. The 2nd MRI at 6 months after first dosing showed a significantly decreased liver fat content from 19.6 ± 8.9% to 15.7 ± 7.6%. ($p = 0.001$). More than half (52.4%) of the patients had improvement of liver fat content and only 19.0% of the patients had worsening liver fat content on the 2nd MRI. Further analysis demonstrated initial higher liver fat content as the only independent factor associated with improvement of liver fat content at 2nd MRI. (OR: 1.22, 95% CI: 1.082–1.369, $p = 0.001$). For histology changes, most of the patients showed none change or improvement in steatosis, NASH grade and stage. Only a few patients (<10%) showed a worsening change in histology.
Conclusion: The preliminary results of the first-in-Asia randomized trial demonstrated insulin sensitizer improved liver fat on MRI and NASH severity on histopathology. Further analysis upon the study deblinding is mandatory to evaluate the efficacy and safety.

FRI102

Efficacy and feasibility of a very low calorie diet to achieve 10% weight loss in patients with advanced non-alcoholic fatty liver disease

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Background and Aims: NAFLD is the most common liver condition worldwide and is directly linked to chronic excess calorie consumption, lack of physical activity and overweight/obesity. In the absence of approved drugs, lifestyle modification promoting weight loss, is the primary recommended therapy for NAFLD. A weight loss goal of ~10% has been recommended for patients with NAFLD as this has been shown to improve liver fat, inflammation and fibrosis. However, only 10–20% of patients achieve this level of weight reduction with standard dietary approaches. This pilot study aimed to determine whether an 8–12 week very low calorie diet (VLCD) is an acceptable therapy to achieve a target weight loss of 10% in patients with advanced NAFLD.

Subject Characteristics	Baseline (n = 30)	Post-VLCD (n = 27)	P-Value
Age (years)	56 ± 12		
Sex (n) male/female	18/12		
Time since NAFLD Diagnosis (months):			
Mean	28.4 ± 31.7		
Median (range)	13.5 (1–113)		
Anthropometry			
Weight (kg)	119 ± 25	104 ± 21	0.000**
BMI (kg/m^2)	42 ± 8	37 ± 8	0.000**
Body fat (%)	45 ± 6.9	40 ± 9.1	0.001**
Blood pressure: Systolic (mmHg)	144 ± 15	133 ± 14	0.003**
Diastolic (mmHg)	86 ± 11	81 ± 9	0.018*
Blood samples			
Total cholesterol (mmol/L)	4.3 ± 0.9	4.3 ± 1.1	0.652
Triglycerides (mmol/L)	2.1 ± 1.8	2.0 ± 1.4	0.156
HDL (mmol/L)	1.2 ± 0.3	1.6 ± 1.9	0.270
AST (IU/L)	35 ± 18	25 ± 9	0.004**
ALT (IU/L)	47 ± 30	31 ± 16	0.003**
GGT (IU/L)	82 ± 74	52 ± 72	0.000**
Fasting glucose (mmol/L)	7.5 ± 2.3	6.1 ± 1.1	0.002**
Hba1c (mmol/mol)	50 ± 13	42 ± 9	0.000**
Insulin (pmol/L)	135 ± 85	92 ± 91	0.018*
Fibroscan			
Stiffness (KPa)	13.0 ± 6.6	8.0 ± 2.9	0.022*
IQR (KPa)	3.5 ± 3.0	2.5 ± 2.8	0.183
Non-invasive scores			
FIB-4	1.5 ± 1.0	1.2 ± 0.7	0.206
QRISK2	15.6 ± 14.2	11.9 ± 9.8	0.030*

Values are means (SD). *significant difference Baseline vs. Post-VLCD ($p < 0.05$); **significant difference ($p < 0.01$).

Method: 30 patients with advanced NAFLD were recruited to an 8–12 week VLCD (~800 kcal/day) using meal replacement products (Optifast, Nestlè Health Science). Anthropometrics, blood tests (liver enzymes, lipid profile, glucose, HbA1c, insulin), liver stiffness and cardiovascular disease risk were measured at baseline and after the VLCD intervention.
Results: Of the 45 patients approached to take part in this study, 30 consented to enrol. This study was fully recruited at a single site within 6 months and 27/30 retained post VLCD.
68% of patients reached the weight loss target of 10%; mean weight loss was 13 kg.
Weight loss through an 8–12 week VLCD significantly improved liver health (liver enzymes and liver stiffness), cardiovascular disease risk (blood pressure and QRISK2) and metabolic health (fasting glucose, HbA1c and insulin). BMI and body composition also improved (See Table 1).
Conclusion: A VLCD is a feasible way of achieving 10% weight loss in patients with advanced NAFLD. Patients were willing to undertake the strict dietary intervention and significant improvements in liver, metabolic and cardiac health were observed.

FRI103

IDL-2965: a selective, highly potent, clinical-stage integrin antagonist for treatment of non-alcoholic steatohepatitis

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Background and Aims: Clinical outcome in NASH is associated with the stage of liver fibrosis. RGD-binding integrins are attractive therapeutic targets for the treatment of fibrosis. IDL-2965 is a potent antagonist of integrins αvβ1, αvβ3, and αvβ6 that is being evaluated in a Ph1/1b clinical study. The present work characterizes the antifibrotic activity of IDL-2965 in animal models of liver fibrosis at exposures attained following oral dosing in clinical studies.
Methods: The effects of oral IDL-2965 on liver fibrosis and fibrosis-related plasma biomarkers were assessed in mouse and rat carbon tetrachloride (CCl_4)-induced liver fibrosis models, a mouse choline-deficient, amino acid-defined, high-fat diet (CDAHFD) model, and a diet-induced obesity (DIO-NASH) model in ob/ob mice. Clinical safety and pharmacokinetics (PK) of IDL-2965 in healthy volunteers were evaluated in single- and multiple-ascending dose studies.
Results: At exposures attained clinically, IDL-2965 strongly inhibits fibrosis in multiple animal models. In a rat model of CCl_4-induced fibrosis, prophylactic treatment with IDL-2965 significantly reduced liver fibrosis (via histopathology). In a mouse CCl_4 model, therapeutic treatment with IDL-2965 provided a greater therapeutic effect than an αvβ1-specific compound. In a mouse CDAHFD model, therapeutic treatment with IDL-2965 significantly reduced fibrosis scores (via histopathology), liver hydroxyproline, and plasma CK-18. In a mouse DIO-NASH model, a comparison of morphometric measures of collagen and αSMA in biopsies taken pre- and post-treatment demonstrated that IDL-2965 reduced pre-existing fibrosis. Pharmacodynamic studies in the DIO-NASH model further demonstrated that IDL-2965 reduced plasma CK-18 and TIMP-1 within one week, with reductions in hyaluronic acid by week 4. In Ph 1 clinical studies in healthy volunteers, once-daily oral administration of IDL-2965 for up to 14 days was safe and well tolerated and achieved robust dose proportional plasma PK that exceeded the maximal efficacious exposure in preclinical fibrosis models at a dose of 45 mg.
Conclusions: At exposures attained following oral administration and associated with a favorable safety profile in healthy volunteers, IDL-2965 exhibits robust antifibrotic effects in multiple models of liver fibrosis. IDL-2965-mediated reductions in liver fibrosis are accompanied by changes in relevant plasma biomarkers. These data support evaluating IDL-2965 in NASH patients.

FRI104

The effectiveness of Mediterranean diet versus calorie restriction in non-alcoholic fatty liver disease (NAFLD): a systematic review with clinical implications

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Background and Aims: Lifestyle interventions that focus on reduced energy intake and improved dietary pattern are the cornerstone of NAFLD management. However, it remains unclear whether a Mediterranean diet (MD) is more beneficial than other diets, or confers benefits beyond weight loss.
Method: A systematic review of trials investigating the effects of MD and calorie-restricted interventions (CRI), on NAFLD was conducted. In February 2019, we searched MEDLINE, Embase, Scopus, WoS, and CENTRAL databases using key words for NAFLD, controlled trials, MD and weight loss. The Cochrane Handbook and risk of bias tools (Rob 2.0/Robin I) were used to assess study quality.
Results: 2173 publications were identified; from these 15 trials with 1725 participants met the inclusion criteria. Study characteristics included: 59% male; mean BMI 30.1 kg/m^2 at baseline, mean follow-up 33 weeks (range 2–104 weeks). Nutritional intake using self-report instruments was described in 8 studies. Hepatic Steatosis (HS) was assessed using histology (n = 1), MRS/MRI-PDFF (n = 5), USnd (n = 7) and FLI (n = 4). Compared with standard care (SC), CRI (n = 10; 1492 participants) improved ALT levels, MRS/USnd/FLI HS and fibrosis markers and resulted in greater weight loss (6.3% (CRI) vs. 0.4% (SC)). Weight loss of ≥ 7% tended to improve HS, lobular inflammation, ballooning injury and NAS, but not a reduction in fibrosis. AST levels decreased in both CRI and SC groups. All CRI produced similar weight losses of 5.2%–6.0% and improved ALT, AST, and USnd HS. However, interventions with specific dietary change components beyond calorie restriction, such as olive oil enrichment, reported larger improvements. MD (n = 5; 233 participants) produced bigger improvements in USnd/FLI HS and fibrosis markers when compared with SC and resulted in greater weight loss of 5.7% vs. 1.1%. ALT levels improved in both MD and SC groups. MD and low-fat diets both improved ALT and MRS/MRI-PDFF HS, with greater HS reductions in MD groups (35.7% vs. 16%), independent of weight loss.
Conclusion: Dietary changes are clinically beneficial for NAFLD. Calorie restriction is effective with a dose-response relationship between effects on liver function and weight loss. Based on the limited evidence available, MD appears to be the diet of choice, with or without weight loss. The mechanisms by which MD exerts its NAFLD-specific effects are poorly understood and need clarification in further experimental studies.

FRI105

Therapeutic efficacy of the chitotriosidase inhibitors in STAM model of non-alcoholic steatohepatitis

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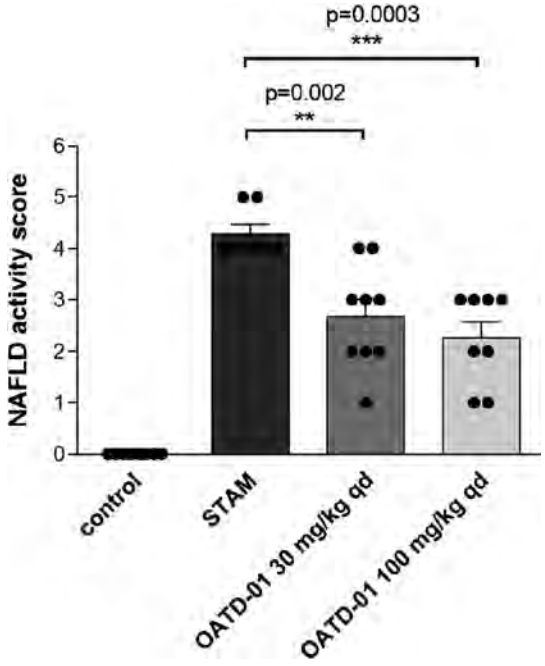
Background and Aims: NASH (non-alcoholic steatohepatitis) is a chronic liver disease characterized by steatosis, inflammation, hepatocytes death, metabolic disfunction and, in severe cases, fibrosis. One of the key players in progression of NASH are Kupffer cells (KCs) – liver resident macrophages. When activated, they initiate cascade of events resulting in canonical pathologies of NASH. Chitotriosidase (CHIT1), a member of the glycosyl hydrolase family 18, is highly and specifically induced in KCs from patients with NASH but not these with simple steatosis. CHIT1 expression significantly correlates with the stage of disease, inflammation and fibrosis. These results prompted us to evaluate therapeutic potential of chitotriosidase inhibition in the STAM model of NASH with OATD-01, a potent, oral, small molecule chitinase inhibitor currently in Ph1 clinical trials for inflammatory and fibrotic lung diseases.
Method: STAM mouse model of NASH was induced by a subcutaneous injection of streptozotocin to 2-day-old mice and following continuous high fat diet. After pathology has developed, animals were treated with a vehicle or OATD-01 at 30 and 100 mg/kg/day. At the end of the study serum and liver samples were collected for biochemical and histological evaluation. Comprehensive histological NAS score (NAFLD activity score – combined scores of hepatocytes ballooning, inflammation, steatosis) was used as a main read-out of severity of NASH.
Results: In the pilot studies we confirmed significant induction of the chitinolytic activity in plasma and expression of CHIT1 in KCs-like cells in livers of the STAM mice. Administration of OATD-01 in the therapeutic scheme significantly decreased the NAS score with a reduction of all 3 pathological parameters, including a strong improvement in hepatocytes ballooning. Additionally, OATD-01 alleviated morphometrically measured fibrosis and a number of F4/80 macrophages. The therapeutic efficacy of OATD-01 in the STAM model correlated with a strong inhibition of the chitinolytic activity (pharmacodynamic marker).



Conclusion: Therapeutic efficacy of OATD-01 in the STAM model represents a preclinical proof-of-concept for the pathological role of CHIT1 in NASH. These results together with the documented clinical correlation of CHIT1 expression with NASH progression provide a rationale for the further development of OATD-01 as a novel therapy for the disease.

FRI106

Endoscopic gastric plication (endosleeve) improves hepatic steatosis and liver fibrosis in patients with grade 1-2 obesity, preliminary results at 6 months

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Background and Aims: There is a higher prevalence of non-alcoholic steatosis/steatohepatitis in patients with obesity. The intragastric balloon is the endoscopic treatment of choice for short-term weight loss. However, endoscopic gastric plication (Endosleeve) may offer better long-term results. Fibrosis and hepatic steatosis (HS) can be estimated non-invasively with transition elastography (TE) and the controlled attenuation parameter (CAP).
Method: Prospective and multicenter pilot study aimed at 1) assessing the safety and efficacy of Endosleeve and 2) its effect on hepatic fibrosis and steatosis (subcohort of patients from Teknon Medical Center (TMC). We included patients with grade I-II obesity and without diabetes mellitus. We use the endoscopic Incisionless Operating Platform™ (USGI Medical, San Clemente, CA, USA), with a defined pattern of transmural plication arrangement with g-Cath™ EZ suture, to reduce gastric volume/distensibility in order to slow down gastric emptying. TE + CAP (Fibroscan®) and blood analysis were evaluated at baseline and at 2 and 6 months (m).
Results: 39 patients were included; 17/39 (44%) patients from TMC were analyzed. At baseline, 88% had grade II obesity with a mean age of 46 ± 7 years (59% women). There were no serious adverse effects related to the endoscopic technique. At baseline, 29% had liver stiffness values compatible with risk zone for fibrosis (ET >8 kPa; mean 9 ± 2) and 71% had HS >10% (CAP >248 dB/m; mean 320 ± 37). At 2 and 6 m there was a media decrease of the total excess weight (TEW) (37 ± 11 and 53 ± 20%, respectively) with amelioration in fibrosis (ET <8 vs >8 kPa, p = 0.01) and HS (CAP <248 vs>248, p = 0.001). In addition, at 6 m there was a decrease in levels of triglycerides (p = 0.01) with an increase in HDL cholesterol (p <0.01).

Total Excess Weight (%)	Body Mass Index (BMI)			Excess Weight Loss (%)		Liver stiffness (kPa)			Liver steatosis (dBm)		
Baseline	Baseline	2 months	6 months	2 months	6 months	Baseline	2 months	6 months	Baseline	2 months	6 months
48	35	31	29	38	51	2,8	3,7	2,5	188	206	230
58	39	33	32	37	47	5,6	3,7	5,8	207	185	240
62	40	37	37	22	19	4,0	3,5	4,9	244	149	205
41	32	29	29	34	37	3,8	4,6	4,1	251	214	176
53	36	31	30	41	42	5,1	2,8	4,9	280	100	236
66	39	32	27	39	73	3,0	3,7	3,8	281	220	173
56	37	30	26	48	83	5,2	6,0	5,6	295	210	223
42	35	30	28	47	70	3,3	4,4	2,7	378	312	239
58	39	35	36	27	24	3,8	4,1	3,6	319	248	242
30	31	27	25	58	83	4,2	3,8	4,5	329	245	234
64	39	34	31	27	47	4,8	4,7	3,6	321	287	214
52	37	32	31	37	46	7,6	6,4	6,8	350	246	271
60	36	32	29	30	52	8,2	6,8	4,6	337	260	220
69	37	30	26	18	43	8,3	6,7	6,4	193	178	160
51	36	33	32	27	36	9,0	4,9	2,4	231	200	213
45	35	30	26	46	87	6,5	7,5	7,4	338	228	266
65	40	32	30	52	61	12,3	11,3	11,1	364	250	160

> 50%	Overweight	25-30	15 - 29	Risk of fibrosis	kPa		dBm	% Steatosis
< 50%	Obesity type I	30-35	30 - 50	No	< 8	S0	< 248	< 10
	Obesity type II	35-40	>50	Yes	> 8	S1	249 - 268	10 - 33
						S2	269 - 280	33 - 66
						S3	> 280	> 66

Conclusion: The Endosleeve offers promising preliminary results at 6 months. It is safe, reduces TEW in a media of 53% ± 20% and is associated with amelioration of fibrosis, HE and dyslipidemia. Long-term follow-up is necessary.

FRI107

Use of GLP-1 receptor agonists (GLP1A) and/or SGLT-2 inhibitors (SGLT2I) in populations with NASH or at risk of NASH in US clinical practice

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Background and Aims: Currently, no drugs are FDA approved for the treatment of NASH. However, some success has been observed with GLP1a in histological resolution of NASH without worsening of fibrosis and with SGLT2i in reduction of body weight, ALT, and FIB4 compared with baseline values. Here, we examined data from type II diabetic (T2DM) and non-T2DM patients with or at risk of NASH to determine use of these therapies in clinical practice.

Method: Data collected from a proprietary US EMR database were limited to adult patients with diagnosed NAFLD without NASH (ICD10 K76 and ICD9 equivalent without evidence of NASH), NASH (ICD10 K75.81) or with a risk profile (RISK) of Age >50 + ALT >30 U/L + [BMI >30 or T2DM] and without viral hepatitis or evidence of alcohol abuse. Index date was assigned at the first calculable FIB4 between Jul 2015 to Jun 2017 and for which >1 year history and >2 years follow-up or to death was available.

Results: Of 30MM adult patients, 81108 met all study criteria with 22% (17582) NAFLD without NASH, 1% (914) NASH, and 77% (62612) RISK (without NAFLD or NASH) [Figure]. At index, 50% (40194/81095) male, 84% (65121/77635) white, 73% BMI >30 (44190/60882), 43% (34730) T2DM, 11% (9210) FIB4 ≥ 2.67, and median (IQR) age 60 (55–65). Use of SGLT2i and GLP1a at index was 2% and 3% respectively overall, but higher in the T2DM subset (4% and 7%) compared to non-T2DM (<1%, $p < 0.001$). Among 105 non-T2DM on SGLT2i, 54% received canagliflozin, 41% dapagliflozin, and 35% empagliflozin. Among 188 non-T2DM on GLP1a at index, 64% received liraglutide, 30% dulaglutide, and 22% exenatide. Non-T2DM patients receiving SGLT2i and/or GLP1a (n = 279) differed from those not on these therapies (n = 46099) in age (mean 57.0 v. 60.5 not treated (NT), $p < 0.001$), Charlson CI (0.9 v. 1.7 NT, $p < 0.001$), AST>30 IU/L (43% v. 36% NT, $p = 0.014$), blood glucose ≥ 1.1 g/dL (66% v. 27% NT, $p < 0.001$), HbA1c ≥ 5.6% (91% v. 72% NT, $p < 0.001$), triglycerides ≥ 150 mg/L (35% v. 25% NT, $p < 0.001$), LDL cholesterol ≥ 100 mg/dL (22% v. 33% NT, $p < 0.001$), and eGFR ≥ 90 (41% vs. 31% NT, $p = 0.001$).

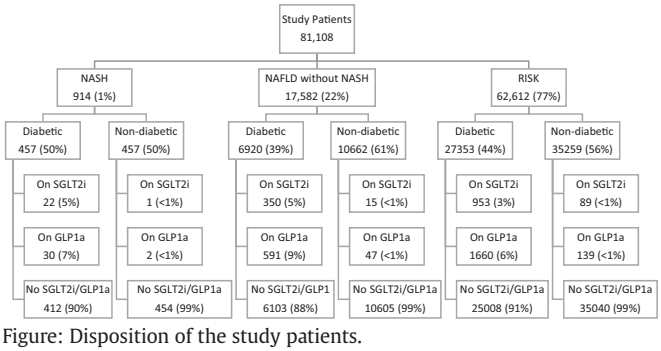

Figure: Disposition of the study patients.

Conclusion: Despite evidence suggesting benefits with GLP1a and SGLT2i in patients with NASH or risk of NASH, real-world use of these therapies in patients with T2DM was relatively low at 4–7% despite higher rates of insurance drug coverage for this population. Use in non-T2DM patients was <1% overall and more common in younger patients with fewer comorbidities and with lab measures similar to T2DM patients.

FRI108

BIO89-100, a novel glycopegylated FGF21 analog, reduces body weight and fat mass in naive CD-1 mice through an increase in energy expenditure despite an increase in food consumption

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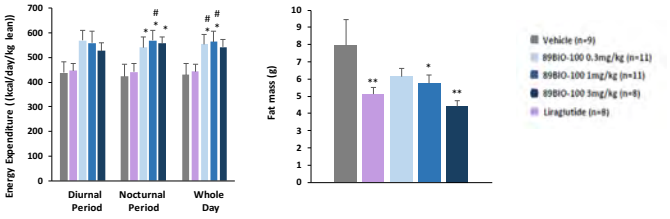
Background and Aims: BIO89-100, a novel glycoPEGylated analog of FGF21, is being developed for the treatment of nonalcoholic steatohepatitis (NASH) and cardiometabolic diseases. In CD-1 mice, BIO89-100 reduces body weight (BW) despite increased food consumption (FC). To better understand these findings, we investigated the effect of BIO89-100 on energy expenditure and body composition.

Methods: Naïve mice were treated subcutaneously (SC) for 4 weeks at ambient temp. with BIO89-100 at doses of 0, 0.3, 1.0 and 3.0 mg/kg (3qW × 4 weeks) or with liraglutide at 0.2 mg/kg (BID × 4W; SC). BW and FC were measured daily throughout the treatment period. To investigate the impact of BIO89-100 on energy expenditure, the respiratory exchanges (VO_2 and VCO_2) were recorded during 3 distinct sessions of METABOpack™, a multiparametric approach allowing an automated and simultaneous recording of FC, water intake, respiratory exchanges and spontaneous activity. Meal pattern analysis was conducted on the high-resolution recordings of FC. The body composition (fat, lean and fluid masses) was analyzed 3 times during the study by the mean of Time-Domain Nuclear Magnetic Resonance (TD-NMR).

Results: Dose-dependent decrease in BW (up to −13.8%) and increase in FC (up to +94%) were observed in BIO89-100-treated mice. Increased FC was related to an increase in mean meal number, with no change in mean meal size. There was no evidence of change in basal metabolism or total spontaneous activity in studied animals, thus the increase in energy expenditure is presumed to be through increased thermogenesis. BIO89-100-treated mice had a marked decrease in fat mass (measured both by TD-NMR during the study and by weighing the epididymal white adipose tissue (eWAT) at sacrifice), without affecting lean masses and body fluid. Liraglutide induced a significant decrease in BW when compared with controls resulting in a final 10% reduction, associated with a decrease in fat mass. However, liraglutide did not affect the energy expenditure or food consumption.



Mean ± SEM. * $p < 0.05$, significantly different vs. Vehicle group; # $p < 0.05$, significantly different vs. Liraglutide group.

Conclusion: Naïve CD-1 mice treated with BIO89-100 had a dose-dependent reduction in BW and increased FC. Our results suggest that this BW loss is due, at least in part, to an increase in energy expenditure, resulting in a marked decrease in fat mass, including the eWAT weight, without affecting lean masses and body fluid. If these effects translate to humans, they could be beneficial in patients with metabolic diseases.

FRI109

EDP-297, a novel and potent fxr agonist, exhibit robust anti-fibrotic effects with significant liver function in a rat model of non-alcoholic steatohepatitis

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Background and Aims: Farnesoid X receptor (FXR) is a nuclear receptor that has emerged as a key regulator in the maintenance of bile acid homeostasis. FXR agonists are currently under clinical investigation for the management of various liver diseases such as primary biliary cholangitis (PBC) and nonalcoholic steatohepatitis (NASH). However, most preclinical studies have examined the effects of FXR agonists in mouse models where fibrosis progression to cirrhosis does not resemble that observed in humans. Here, we investigate the anti-fibrotic effects of the FXR agonist EDP-297 in a rat model of NASH cirrhosis.
Method: Adult male Wistar rats (175–200 g) were fed either normal chow (NC) or a choline-deficient, L-amino-acid-defined, high-fat diet with 60 kcal% fat and 0.1% methionine (CDAHFD) for 12 weeks. Rats were randomized to receive either vehicle control (0.5% methylcellulose (MC)), 0.1 mg/kg EDP-297, or 0.3 mg/kg EDP-297 by once-daily oral gavage at the first signs of fibrosis (5 weeks, n = 8 per group).
Results: Treatment with EDP-297 significantly reduced fibrosis progression as assessed by morphometric quantification of the collagen proportional area using Sirius Red staining (NC 3.0 ± 0.9%; MC 18.4 ± 4.1%; EDP-297 0.1 mg/kg 12.2 ± 3.7% with $p < 0.001$ compared to MC; and EDP-297 0.3 mg/kg 11.9 ± 3.8% with $p < 0.001$ compared to MC). EDP-297 at 0.1 mg/kg also significantly decreased the fat content quantitated by H&E staining (MC 36.1 ± 3.5% vs EDP-297 0.1 mg/kg 26.8 ± 5.0%, $p < 0.001$). Moreover, EDP-297 improved significantly liver function measured by key biomarkers (Table 1).

Table 1: EDP-297 improved significantly liver function measured by key biomarkers

Key Biomarkers	Vehicle Control	EDP-297	Reduction (%)	*p*-value
Alanine Transaminase (ALT, U/I)	547.6 ± 190.7	115.8 ± 37.4	78.9% ↓	$p < 0.001$
Aspartate Aminotransferase (AST, U/I)	1309.0 ± 551.9	347.0 ± 103.5	73.5% ↓	$p < 0.001$
Total Bilirubin (U/I)	0.74 ± 0.32	0.18 ± 0.07	75.7% ↓	$p < 0.001$

Conclusion: In a rat model of NASH cirrhosis that more closely resembles the human disease progression, EDP-297 at a low dose significantly reduced fibrosis progression and improved liver function. These results suggest that EDP-297 may have a potent anti-fibrotic effect in NASH patients, including those with late-stage F3/4 fibrosis.

FRI110

Characterization of EYP001 a novel, potent and selective FXR agonist in in vitro 3D human liver models of NASH

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is a condition defined by excessive fat accumulation (steatosis) in the liver that currently affects 20–40% of the general population. Non-alcoholic steatohepatitis (NASH), the most severe form of NAFLD, is characterized by steatosis, hepatocyte ballooning, inflammation, and fibrosis. It may also lead to complications such as cardiovascular disease, cirrhosis, liver failure or liver cancer. 10–20% of NAFLD patients develop NASH, thus making NASH a significant health burden with currently no approved pharmacological treatments. The Farnesoid X receptor (FXR), a nuclear receptor, controls bile acid homeostasis and is a promising target for the treatment of NASH. EYP001, a novel non-steroidal, selective, potent, second generation FXR agonist, is currently in a phase 2 NASH clinical trial. With this study we aimed to investigate the effects of EYP001 in *in vitro* 3D human liver models of NASH.
Method: Cytotoxicity in 3D InSightTM human liver microtissues was assessed upon exposure to EYP001 and OCA (0.03 to 30 µM) for 7 days. Bile acid secretion profiles were analyzed at day 2 by LC/MS. EYP001 effects predictive of protection against NASH were assessed in 3D bioprinted ExVive human liver tissues following 21 days of daily treatments. PLIN2 and αSMA positive areas were digitally quantified via ImageJ, and ballooning was semi-quantitatively assessed.
Results: EYP001 was found not to be cytotoxic to 3D InSightTM human liver microtissues (as measured by LDH and cellular ATP) throughout the 7 day treatment. Unlike EYP001, OCA showed cytotoxicity at 3 and 10 µM at day 2. Both compounds showed a dose-dependent decrease in secretion of the bile acids GCA and GCDCA within days 0–2. Maximal inhibitory effect on bile acid release was reached at 0.1 and 1 µM for EYP001 and OCA respectively. In 3D bioprinted ExVive human liver tissues, EYP001 reduced PLIN2 (steatosis marker) positive area in a dose dependent manner compared to the untreated NASH control thereby suggesting a decreased presence of lipid droplets with EYP001. Also, EYP001 significantly reduced αSMA (fibrosis marker) positive areas, suggesting potent inhibition of stellate cell activation.
Conclusion: The non-steroidal FXR agonist EYP001 was shown to be well tolerated by 3D human liver tissues *in vitro* and to be more potent than OCA on reduction of bile acid secretion. EYP001 reduced PLIN2 and αSMA, two parameters linked to lipid accumulation and fibrosis respectively, strongly suggesting an improvement of NASH parameters in this 3D *in vitro* human liver model. Based on these preclinical efficacy findings, and safety, tolerability, pharmacokinetics and pharmacodynamics data obtained in Phase 1 clinical trials, EYP001 has now entered a Phase 2 clinical trial examining benefit in NASH patients.

FRI111

Synergistic effect of clostridium butyricum miyairi on rifaximin in mice model of non-alcoholic steatohepatitis by methionine choline-deficient diet

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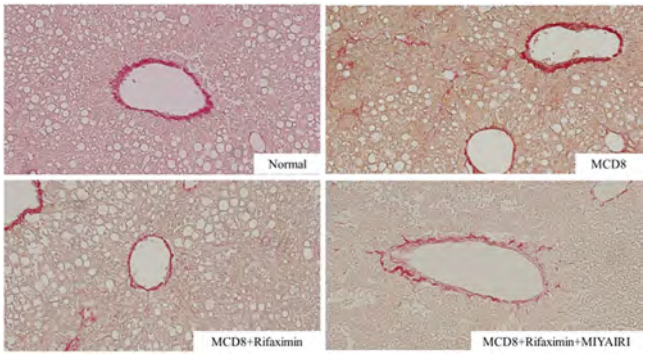
Background and Aims: Nonalcoholic steatohepatitis (NASH) is increasing and recent studies reveled gut microbiota was associated with liver damage. Rifaximin is an anti-absorbable antibacterial agent and widely used as a therapeutic agent for minimal hepatic encephalopathy. We investigated whether the administration of rifaximin and Clostridium butyricum Miyairi (MIYAIRI) improve the hepatic inflammation and fibrosis by NASH.
Method: C57BL/6J mice were fed standard chow or Methionine choline-deficient (MCD) diet for 8 weeks. We divided into four groups (1) standard chow, (2) MCD, (3) MCD + rifaximin, and (4) MCD + rifaximin + MIYAIRI. Mice were followed for 8 weeks while rifaximin was administered at 0.012 mg/kg/day and/or MIYAIRI

0.024 mg/kg/day from 5 to 8 weeks. Inflammation and fibrosis were evaluated in liver, intestine, and mesenteric lymph node (MLN).
Results: In the MCD diet group, the expressions of IL- 6 and TNF-alpha increased in small intestine, MLN and liver. The expression of TGF-beta in liver was also upregulated. The administration of rifaximin alone did not improve the hepatic inflammation and fibrosis in NASH models. However, the use of rifaximin + MIYAIRI significantly suppressed the hepatic inflammation and fibrosis compared with rifaximin alone. The expression of IL- 6 and TNF-alpha MLN and liver, TGF-beta liver and CLDN1 in small-intestine was downregulated in rifaximin +MIYAIRI group than rifaximin.



Conclusion: Our results suggested that the gut microbioma was involved in the pathogenesis of NASH and hepatic inflammation and fibrosis could be more suppressed by Butyrate-producing bacteria as MIYAIRI in addition to anti-absorbable antibacterial agent.

FRI112

Methylnaltrexone and rifaximin treatments significantly improve chronic "leaky gut" in a diet-induced mouse model of non-alcoholic fatty liver disease

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Background and Aims: Increased gut permeability (GP, "leaky gut") occurs in the progression of numerous diseases, such as nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH) and hepatic encephalopathy. These conditions are partially driven by proinflammatory bacterial products leaking from the gut into the bloodstream. The aim of this study was to evaluate the mu-opioid receptor antagonist methylnaltrexone (MNTX) and the nonsystemic antibiotic rifaximin for improving GP in a diet-induced animal model of nonalcoholic fatty liver disease (DIAMOND), which develops chronic leaky gut and progressive NASH when fed a Western diet (WD).
Method: Four groups of 8 DIAMOND mice were initially fed a WD (Teklad 42% kcal from fat and 4% sugar water) for 8 weeks then continued on a WD with concomitant oral gavage administration of aqueous vehicle, MNTX 25 mg/kg, rifaximin 400 mg/kg, or pioglitazone 30 mg/kg 5 times per week for 12 weeks. GP was assessed at Weeks 12 and 20 by administering 4 kDa dextran 600 mg/kg orally, and followed by dextran quantitation in serum using a competitive ELISA; increased gut permeability correlates positively with serum dextran concentration. Results between groups were compared using Student's 2-tailed t-test, and pair-wise analysis was performed on serial measurements at Weeks 12 and 20 to assess drug treatment effect on GP.
Results: Mean serum dextran concentrations of vehicle WD mice at Week 12 (corresponding to NASH F0) averaged 247 mcg/mL. In the MNTX group, mean serum dextran concentration at Week 12 (4 weeks of treatment) was 90.9 mcg/mL, a 2.7-fold reduction compared with the vehicle group ($p \leq 0.046$). At Week 20 (12 weeks of treatment), mean serum dextran concentrations were 2-fold lower vs the vehicle group for MNTX and rifaximin ($p \leq 0.014$ and $p \leq 0.017$, respectively). Pioglitazone, the active comparator, also improved GP vs vehicle at Week 20. By pair-wise analysis, rifaximin treatment continued improving the leaky gut induced by diet over time; Week 20 serum dextran in the rifaximin-treated group averaged 85.9 mcg/mL compared to the 12-week average of 154.0 mcg/mL. Thus, rifaximin improved leaky gut by 45% in the 8 weeks between the first and second measurement ($p \leq 0.053$).
Conclusion: This preclinical study showed that MNTX and rifaximin treatments dramatically improved WD-induced GP, suggesting that these compounds may have broad utility in treating inflammatory diseases exacerbated by "leaky gut." Further dose optimization studies are needed to determine if these compounds could be effective in NASH. These results support the biological rationale for further testing for efficacy in NASH, particularly in combination with drugs that target other mechanistic drivers of NASH, such as insulin sensitivity and inflammation.
Supported by Salix Pharmaceuticals.

FRI113

Recombinant glutamine synthetase (AM-535): a novel therapeutic approach for the treatment of hyperammonaemia and its deleterious effects on multiple systems

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Background and Aims: Hyperammonaemia is central to the development of hepatic encephalopathy in a spectrum of disorders from liver failure to urea cycle disorders (UCD) but its deleterious effect on the kidneys, lipids and lipids is unknown. We have recently shown that AM-535 directly reduces ammonia in models of cirrhosis, UCD and NAFLD. We developed a new model of diet-induced hyperammonaemia in healthy mice and aim to evaluate the effect of AM-535 on ammonia levels and its end organ effects in this 'pure' model.
Method: Male C57BL mice were fed daily with an isoleucine deficient amino acid mixture (AA), hyperammonaemic diet for two weeks (10 mg/kg) and administered a single dose of vehicle (AAv) or AM-535 (AAGS) (30 mg/Kg), or sodium phenylacetate (SP; 0.3 mg/Kg) (n = 5/group); Controls (C): n = 8. Animals were sacrificed 3 h after a single treatment. Arterial plasma ammonia (NH3), liver and renal function, glucose and lipid profile were assessed. Distribution of AM-535 to the brain and liver was assessed using immunohistochemistry.
Results: Significantly higher ammonia concentrations were observed in AA group compared with controls and this was significantly reduced with AM-535 (AAv: 167 ± 71.64 vs C: 49 ± 9.18 vs AAGS: 70 ± 17.47 μmol/L) ($p < 0.005$). Ammonia concentrations were restored in presence of SP (124.2 ± 37.9 μmol/L; $p < 0.005$) (Figure 1). The reduced AM-535 ammonia levels were also associated with significantly lower urea, creatinine, glucose, HDL cholesterol and albumin (Table 1). No effect of GS was observed in levels of ALT and AST. Liver immunohistochemistry for GS showed perivenular distribution of AM-535 and absence of increased GS brain expression.

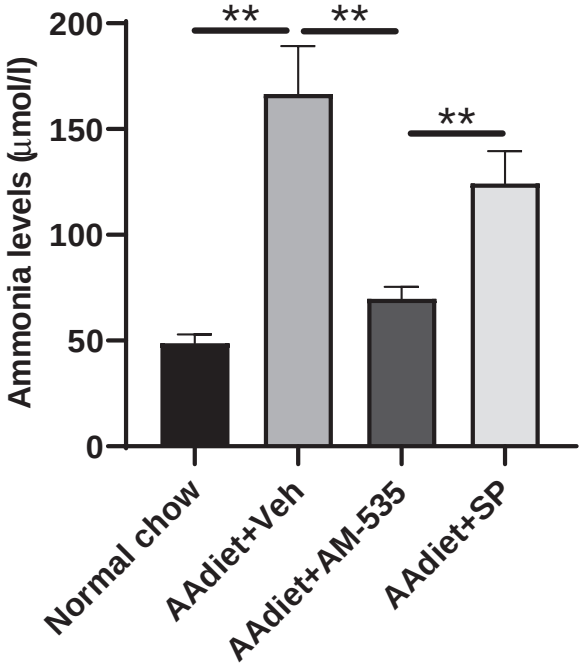

Figure 1: Ammonia levels under controls, recombinant glutamine synthetase (AM-535) and sodium phenylacetate (SP) treatments.

Table 1: Summarised Liver function test analysis

	Normal chow	AAdiet +Veh	AAdiet +AM-535	AAdiet +SP	p value (Normal chow vs AAdiet +Veh)	p value (AAdiet +Veh vs AAdiet +AM-535)	p value (AAdiet +AM-535 vs AAdiet +SP)
Urea (mmol/L)	7.7 ± 0.7	12.1 ± 0.8	8.0 ± 0.8	11.7 ± 1.7	<0.0001	<0.0001	0.0001
Creatinine (µmol/L)	9.2 ± 1.1	8.6 ± 1.0	7.1 ± 1.8	9.6 ± 1.1	ns	0.0380	0.0183
Albumin (g/L)	20.8 ± 2.8	21.9 ± 3.9	21.6 ± 2.8	22.2 ± 3.3	ns	<0.0001	0.0004
Glucose (µmol/L)	16.8 ± 2.3	19.8 ± 1.2	13.4 ± 1.4	13.2 ± 0.6	0.0050	<0.0001	ns
HDL-C (mg/dL)	80.4 ± 3.9	36.7 ± 4.1	45.8 ± 3.9	47.0 ± 4.9	<0.0001	<0.0001	ns

Conclusion: The results of this study show for the first time that induction of hyperammonaemia in an otherwise healthy mouse results is hyperglycemia, hypoalbuminemia and lipid abnormalities. Administration of AM-535 led a rapid reduction in ammonia levels and this was associated with improvement glucose levels, lipid profile, ureagenesis and in renal function. Taken together, these data confirm the safety and efficacy of AM-535 and, provides the rationale for development of this agent for clinical trials.

FRI114

Co-administration of PF-05221304 and PF-06865571 delivers robust whole liver fat reduction and mitigation of acetyl-coa carboxilase inhibitor induced hypertriglyceridemia in patients with NAFLD

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Background and Aims: Disordered lipid metabolism contributes to the pathogenesis of NAFLD/NASH. Acetyl-CoA carboxylase (ACC) and Diacylglycerol acyl transferase 2 (DGAT2) play critical and complementary roles in hepatic lipid metabolism. PF-05221304 (ACCi), a liver directed ACC1/2 inhibitor, and PF-06865571 (DGAT2i), a DGAT2 inhibitor are in clinical development for NASH. Co-administration of ACCi and DGAT2i has potential to re-balance the elevated lipogenic tone in NAFLD/NASH by inhibiting de novo fatty acid synthesis, promoting fatty acid oxidation, inhibiting triglyceride (TG) formation and by down-regulating expression of lipogenic genes. This clinical study was designed to test the hypothesis that co-administration of ACCi and DGAT2i may lead to increased clinical efficacy in the treatment of NASH and mitigation of ACCi-induced TG elevations.
Method: 99 subjects with NAFLD (>8% Whole Liver Fat [WLF] by MRI-PDFF) were randomized and 85 subjects completed the trial. Subjects were stratified by presence or absence of diabetes and baseline WLF. Randomized participants received placebo (N = 14), ACCi 15 mg (N = 29), DGAT2i 300 mg (N = 28) or ACCi 15 mg + DGAT2i 300 mg (N = 28) every 12 hrs for 6 weeks.

	Week 6 Percent Change from Baseline [LS Mean (90%CI)]			
	Placebo	ACCi	DGAT2i	ACCi + DGAT2i
WLF PDFF	N = 12 8.14 (−8.56, 27.89)	N = 22 −40.01 (−47.00, −32.09)	N = 24 −30.14 (−37.97, −21.33)	N = 26 −40.13 (−46.58, −32.90)
Serum TG	N = 12 7.38 (−8.06, 25.41)	N = 22 58.17 (41.76, 76.48)	N = 24 −1.89 (−11.94, 9.32)	N = 26 13.83 (2.27, 26.69)
ALT	N = 12 −3.01 (−11.76, 6.61)	N = 22 −12.41 (−18.24, −6.18)	N = 24 −4.15 (−10.30, 2.42)	N = 24 −7.91 (−13.80, −1.61)
HDL-Cholesterol	N = 12 −3.19 (−9.87, 3.98)	N = 22 −15.56 (−19.70, −11.20)	N = 24 −13.43 (−17.62, −9.03)	N = 26 −18.21 (−22.13, −14.09)
LDL-Cholesterol	N = 12 2.04 (−9.52, 15.09)	N = 22 −19.74 (−26.24, −12.67)	N = 24 −5.22 (−12.81, 3.02)	N = 26 −9.45 (−16.68, −1.59)

Results: Incidence of treatment emergent adverse events was similar across all active treatment groups. No treatment-related SAEs were reported. Pharmacodynamic observations are summarized below.
Conclusion: Co-administration of ACCi+DGAT2i for 6 weeks resulted in greater reductions in WLF than DGAT2i monotherapy and was safe and well-tolerated in adults with NAFLD. ACCi-induced TG elevation was observed and was mitigated by co-administration with DGAT2i after 6 weeks. Decreases from baseline were observed in alanine aminotransferase (ALT), HDL-Cholesterol and LDL-Cholesterol in the ACCi+DGAT2i group, relative to placebo. Aspartate aminotransferase (AST) and alkaline phosphatase were unchanged at 6 weeks (data not shown). These results suggest that additional studies are warranted to assess the potential of ACCi+DGAT2i for the treatment of NASH.

FRI115

A randomized, double-blinded, placebo-controlled single ascending dose study to assess safety, tolerability, immunogenicity, and pharmacokinetics of a novel long-acting GLP-1/GIP/glucagon triple agonist (hm15211) in healthy obese subjects

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Background and Aims: HM15211 is a novel long-acting GLP-1/GIP/Glucagon triple-receptor co-agonist with extended half-life through reduced renal clearance. HM15211 has shown therapeutic potential in animal models of obesity and NASH.
Method: This study was a randomized, double-blind, placebo-controlled First-In-Human trial designed to assess safety, pharmacokinetics, pharmacodynamics, and immunogenicity of a single subcutaneous dose of HM15211 in obese but otherwise healthy adult subjects (Total 41 subjects were randomized, the mean age was 45.7 years, 51.2% were males, and the mean BMI was 33.6 kg/m^2). Subjects were randomized to one of 5 sequential ascending doses of either HM15211 or matching placebo.
Results: HM15211 was safe and well-tolerated in this population without significant changes in physical exams, CV parameters (HR, BP, ECG), and clinical laboratory tests. The most common adverse events were gastrointestinal disorders, reported by 9 out of 31 (29.0%) active subjects. There was no subject who discontinued the study and

there were no serious adverse events due to study medication. A total of 12 out of 31 (38.7%) active subjects tested positive for anti-drug antibodies (ADAs), however, no dose-related trend or relationship between immunogenicity and pharmacokinetic or safety outcomes were observed. Plasma concentration of HM15211 reached its peak level (T_{max}) in 31.20 to 68.08 hours. Plasma $AUC_{0\text{-}inf}$ and C_{max} increased in a dose-proportional manner and the terminal half-life ($t_{1/2}$) was 72.09 to 142.10 hours.
Conclusion: In conclusion, single doses of HM15211 were safe and well-tolerated, and the majority of adverse events were mild and transient. Pharmacokinetic profiles were suitable for weekly administration. Clinical studies in patients with NAFLD/NASH are following.

FRI116
Change in hepatic output of palmitic acid after weight loss in type 2 diabetes
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Background and Aims: Saturated fatty acids and related lipid intermediates contribute to the pathogenesis of NAFLD. Palmitic acid, the most abundant saturated fatty acid, has reported to have toxic effects on insulin signaling and beta cell function. We aimed to assess the change in hepatic output of palmitic acid following weight loss and remission of type 2 diabetes.
Method: 54 participants from the Tyneside cohort of DiRECT: The Diabetes Remission Clinical Trial were studied over 2 years (25/29 F/M, 53.1 ± 1.0 years, and 101.0 ± 2.4 kg). Hepatic palmitic acid production rate (hepatic output) was assessed from the increment in plasma VLDL-TG concentration by a competitive non-isotopic method. Palmitic acid was quantified by GC-MS using FAME method. Liver fat was quantified by 3-point Dixon MRI.
Results: At baseline, liver fat was elevated in this cohort with early diabetes compared with a group of non-diabetic controls (16.4 ± 1.4 v 4.4 ± 1.1%, $p < 0.0001$). After weight loss, liver fat was normalized (3.2 ± 0.5%, $p = 0.65$ vs. control). Hepatic VLDL-TG production rate was also higher (9.7 ± 0.45 vs. 7.9 ± 0.48 mg/L/min, $p = 0.011$), but this was also decreased after intervention (7.8 ± 0.41 mg/L/min; $p < 0.0001$).
Palmitic acid content of fasting plasma VLDL was high in diabetes (11.3 ± 0.8 vs. 7.7 ± 0.8 mg/l, $p = 0.002$). However, hepatic output of VLDL palmitic acid was not different (140.9 ± 7.9 vs. 130.3 ± 8.8 µg/L/min; $p = 0.59$). Fasting plasma VLDL- palmitic acid decreased after weight loss (to 9.4 ± 1.0 mg/l, $p = 0.027$), and as did hepatic output of palmitic acid (to 108.9 ± 6.5 µg/L/min, $p = 0.005$). The change in fasting VLDL-palmitic acid was only significant in those who achieved remission of diabetes whereas hepatic VLDL palmitic acid output decreased irrespective of remission ($p < 0.05$). At 24 months, those who initially achieved remission of diabetes then returned to diabetic state were characterized by higher fasting VLDL-palmitic acid than those in remission (17.1 ± 2.4 vs. 7.6 ± 1.1 mg/l, $p = 0.002$; $p = 0.004$ compared with non-diabetic controls). Paradoxically, hepatic output of palmitic acid was not different between relapsers and those who remained in remission (104.4 ± 19.3 vs.134.2 ± 15.9 µg/L/min, $p = 0.40$).
Conclusion: These data highlight the importance of clearance of plasma VLDL palmitic acid rather than hepatic output in the pathogenesis of this disease. Further work is required to define why clearance of VLDL- derived palmitic acid is impaired in type 2 diabetes.

FRI117
GLP-1/glucagon dual receptor agonist ALT-801 is superior to semaglutide in improving NASH endpoints in a biopsy-confirmed DIO mouse model
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Background and Aims: Body weight loss of approximately 10% improves the metabolic derangements and liver disease in the majority of NASH patients, suggesting metabolic modulators may be effective in the control of the disease. GLP-1 agonists show promise for NASH, but weight loss associated with these agents has been modest. Glucagon receptor activation has direct effects on lipolysis, basal energy expenditure and liver lipid metabolism, so may act synergistically with GLP-1 in the treatment of NASH. To evaluate this hypothesis, we compared ALT-801, a balanced and long-acting GLP-1/glucagon receptor dual agonist, and semaglutide, a GLP-1 agonist, in a biopsy-confirmed DIO NASH mouse model.
Method: Male C57BL/6J mice were fed an AMLN diet high in trans-fat, fructose and cholesterol for 32 weeks. Animals with biopsy-confirmed steatosis (score ≥ 2) and fibrosis (stage ≥ 1) received ALT-801 (10 nmol/kg; SC), semaglutide (10 nmol/kg; SC), or vehicle (SC) for 12 weeks while maintained on the diet. Study endpoints included body and liver weight, liver and plasma total cholesterol (TC) and triglycerides (TG), plasma alanine aminotransferase (ALT), and histological analysis of liver inflammation (galectin-3) and fibrosis (Collagen1a1). Furthermore, within-subject evaluation of changes in composite NAFLD Activity Score (NAS) were performed. Finally, liver RNA sequencing analysis was performed to evaluate the regulation of genes involved in NASH pathways.
Results: ALT-801 demonstrated statistically superior reductions ($p \leq 0.05$) in body weight, liver weight, plasma ALT, liver TG and TC, and plasma TC compared to semaglutide, with only the ALT-801 group returning to normal lean mouse body weight, liver weight and ALT levels. Reduction in the inflammation marker galectin-3 was also superior to semaglutide, with a numerically greater reduction in the fibrosis marker COL1a1. In addition, all animals treated with ALT-801 improved composite NAS driven by reduction in steatosis, lobular inflammation and hepatocellular ballooning scores. Principal component analysis of the 500 most variable genes differentially clustered genes regulated by ALT-801 from those regulated by semaglutide consistent with a unique gene regulatory signature associated with glucagon receptor activation. ALT-801 also resulted in suppression of archetypal genes involved in de novo lipogenesis and fatty acid uptake (FASN, GPAT2, CD36), inflammation (jun, fos, p38, TLR4), hepatocellular death (AIM2, CASP1, IPAF, RIP3), fibrosis (collagens, TIMPs, MMPs) and stellate cell activation (A-SMA, CD146, PDGF, TGF-β).
Conclusion: This study provides evidence for the beneficial effects of glucagon receptor activation in the therapeutic treatment of NASH. The return of body weight to lean normal and metabolic improvement with improvement of liver pathology highlights ALT-801 as a new candidate for the treatment of NASH.

FRI118
Long-term safety profile of cenicriviroc in adults with non-alcoholic steatohepatitis: rollover study
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Background and Aims: Pharmacologic treatments for nonalcoholic steatohepatitis (NASH) need to display a good long-term safety and tolerability profile. Cenicriviroc (CVC), a novel, oral and potent inhibitor of C-C chemokine receptor types 2 and 5, is currently being evaluated for the treatment of liver fibrosis in adults with NASH. In the Phase 2b CENTAUR study (NCT02217475), CVC treatment resulted in a significant antifibrotic benefit over placebo in the Year 1 primary analysis with an excellent safety profile. The aim of this analysis was to assess the long-term safety profile of CVC in subjects from CENTAUR included in the Rollover study (NCT03059446).
Method: Rollover is an ongoing, open-label, multicentre global study of CENTAUR completers as well as subjects who have met pre-specified adjudicated events in the ongoing Phase 3 AURORA study (NCT03028740). CENTAUR completers were analysed by total treatment duration across CENTAUR and the Rollover study. The safety endpoints include clinical laboratory assessments of interest and adverse events (AEs). AEs were coded using the Medical Dictionary for Regulatory Activities version 22.0. Treatment relatedness was assessed by the investigator.
Results: As of 7 October 2019, a total of 147 subjects have been enrolled in the Rollover study, 106 of whom were previously on CVC in CENTAUR. Over time, the incidence rates of treatment-related AEs and serious AEs (SAEs) did not increase with longer treatment durations (Table). In subjects treated for 24 to <36 months and 36 to <48 months, no differences in gastrointestinal AEs (38.9% and 40.8%, respectively) and AEs of infections/infestations (38.9% and 38.8%, respectively) were observed. Only one subject discontinued CVC due to liver biochemistry elevations, which was adjudicated as not related to CVC by an external expert panel.
Table: Summary of AEs

n (%)	All AEs	Treatment-related AEs	SAEs
Overall (N = 106)	84 (79.2)	11 (10.4)	18 (17.0)
0–24 mos (n = 6; 5.7%)	3 (50.0)	0	1 (16.7)
24 – <36 mos (n = 36; 34.0%)	29 (80.6)	5 (13.9)	4 (11.1)
36 – <48 mos (n = 49; 46.2%)	38 (77.6)	5 (10.2)	9 (18.4)
48 – <60 mos (n = 15; 14.2%)	14 (93.3)	1 (6.7)	4 (26.7)

Conclusion: This is the first presentation of safety data beyond 36 weeks for NASH treatment. These data suggest that CVC's safety and tolerability profile in patients with NASH and liver fibrosis remained favourable with chronic exposure beyond 2 years. Writing assistance by Complete HealthVizion.

FRI119
Novel autophagy inducer, a4368 improves non-alchoholic steatohepatitis in mice

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Background and Aims: Recently, impaired autophagy has been reported to be critically associated with the progression of non-alcoholic steatohepatitis (NASH). Here, we investigated whether A4368, an autophagy inducer, has a therapeutic effect on NASH.
Method: A4368 was selected from a focused chemical library as an effective autophagy inducer. After A4368 treatment in Hep3B cells, LC3-II formation and the expression of inflammatory genes were monitored by western blotting and RT-qPCR. The efficacy of A4368 was investigated in high-fat diet (HFD) and STAMTM mice models. In HFD model, C57BL/6N mice were fed with high-fat diet (HFD, 40% Fat + 20% fructose + 2% cholesterol) for 35 weeks to induce NASH and were orally administered with 10, 25, or 50 mg/kg of A4368 for 8 weeks. In STAMTM model, C57BL/6N mice were subcutaneously injected with 0.2 mg streptozotocin 2 days after birth and fed with high fat diet (57kcal% fat) from 4 to 9 weeks of age. A4368 was orally administered for 4 weeks. We evaluated the therapeutic potential of A4368 by testing steatosis, fibrosis, and elevated liver enzymes such as ALT and AST and cholesterol levels in blood. To evaluate pharmacokinetics and tissue distribution, A4368 was orally administered in ICR mice. The concentration of A4368 was quantitatively analyzed in plasma and tissues by LC-MS/MS.
Results: A4368 increased autophagy flux in Hep3B. In addition, the expression of inflammatory genes was significantly suppressed by A4368 treatment. In HFD model, histological analysis revealed that A4368 treatment markedly decreased hepatic steatosis in a dose-dependent manner and reduced lobular inflammation and hepatocyte ballooning (25 mg/kg). Based on these observations, A4368 treatment improved NAS score (NAFLD activity score). However, increased body weights of HFD-fed mice were not reduced by A4368 treatment. To further evaluate the therapeutic activity in fibrosis, collagen deposition was evaluated using Sirius red staining, and hydroxyproline assay. The treatment of A4368 significantly decreased the fibrosis area and the amount of hydroxyproline. A4368 also showed comparable NAS score and reduction of fibrosis area with OCA in STAMTM mice. In a pharmacokinetic study, A4368 showed selective liver-targeting PK profile and only trace amounts were detected in other tissues.

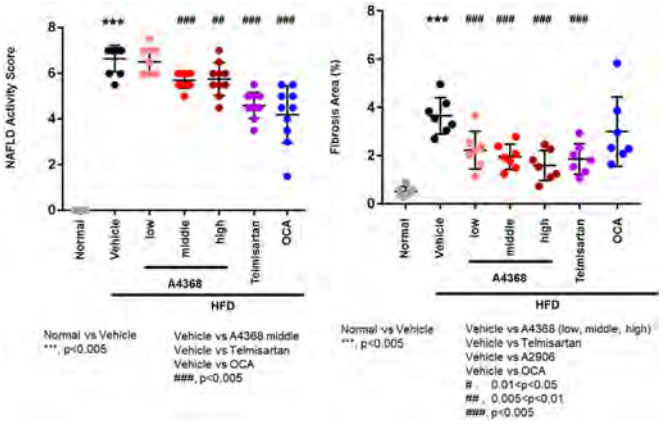

Figure: Improvements of NAS score and fibrosis by A4368 in HFD model.

Conclusion: Taken together, A4368 has therapeutic effect in NASH with selective liver targeting.

FRI120
Intrahepatic microcirculation disorders and increased blood ammonia at the chronic liver diseases with initial stage of liver fibrosis

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Background and Aims: ammonia is new therapeutic target for chronic liver diseases. Some experimental studies demonstrated effect of hypoammoniemic drugs for decrease of activity of hepatic stellate cells, improvement of endothelial function, liver microcirculation and prevention of liver fibrogenesis. Aims of our study are to estimate blood level of ammonia, intrahepatic microcirculation and

efficacy of Hepa-Merz (L-ornithine-L-aspartate) for correction of such disorders at the chronic liver diseases.
Method: We investigated 26 nonalcoholic steatohepatitis (NASH) and 35 HCV patients with initial fibrosis 0–2 stages. Level of ammonia was estimated by biochemical method (PocketChem BA, Arcray, Japan) in capillary blood at the patients and 19 healthy individuals (control). Intrahepatic hemodinamics are determined by polyhepatography (PHG) - modificated hepatic impedansometry, non-invasive method for integral estimation of intrahepatic blood flow by checking of tissue resistance to weak electric current. PHG registers a blood flow in projection of zone of hepatic right, left lobes and spleen, integral body impedansography. For verification of functional disorders in during PHG we use test with deep respiration and nitrates. For correction of blood flow disorders we used hypoammoniemic drug Hepa-Merz in dosage 3 grams 3 times daily 4 weeks. Efficacy of LOLA we looked in 2 and 4 weeks via the control PHG and control of ammonia.
Results: Analysis of PHG demonstrated, that at all patients we revealed a liver microcirculation disorders - increased blood resistance, abnormal forms and amplitude of waves in sinusoidal level (out flow zone) at NASH patients and presinusoidal level (inflow zone) at viral patients. Level of ammonia was higher in the patients compared with control group ($p < 0.001$), and hyperammoniemia was higher at the NASH patients ($p < 0.01$). Analysis of efficacy of Hepa-Merz showed, that it was effective for correction of hepatic hemodinamic disorders, in 2 weeks of the treatment we observed normalization or improvement of the wave form, in 4 weeks – wave amplitude. Level of ammonia was decreased in 2 weeks.
Conclusion: chronic liver diseases with initial liver fibrosis, especially NASH, are characterized by hyperammoniemia, disorders of intrahepatic microcirculation. LOLA improved liver microcirculation and decreases of blood ammonia level at the NASH and HCV patients.

FRI121
Composite targeting of nuclear receptors protects against diet-induced NAFLD

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Background and Aims: As key regulators of hepatic metabolism, bile acid-activated receptors impact on non-alcoholic fatty liver disease (NAFLD) pathogenesis, supporting the use of selected agonists to treat disease. To this end, ligands of the farnesoid X receptor (FXR) and G protein-coupled receptor 5 (TGR5) are promising, although their efficacy is still limited and accompanied by side effects. Here, we aimed to elucidate whether INT-767, a dual FXR and TGR5 agonist, alone or in combination with miR-21 silencing, could synergize in ameliorating NAFLD and its progression towards hepatocellular carcinoma.
Method: C57BL/6N mice were fed a high-fat choline-deficient (HFCD) diet for 14 or 24 weeks, supplemented with or without INT-767, and/or injected with antagomiR-21 or a scrambled antagomir (control). Liver and serum samples were collected and processed for histological and molecular assessment. Expression of genes and proteins involved in NAFLD signalling circuits, as well as those lying downstream of activation of nuclear receptors were investigated through qRT-PCR and immunoblotting.
Results: 14-week HFCD-fed mice developed non-alcoholic steatohepatitis (NASH) with minimal fibrosis, whereas 24-week-fed animals already displayed significant fibrosis and, notably, pre-neoplasic nodules. Noteworthy, INT-767 and antagomiR-21, alone or in combination, prevented disease progression at both time points. Particularly, HFCD diet-induced upregulation of liver pro-inflammatory genes and proteins, as well as pro-fibrogenic markers, were significantly reverted by either INT-767 or antagomiR-21 alone, and even more so, by both treatments combined. Similar results were observed in histological examinations. Further, HFCD diet-induced downregulation of lipid metabolism genes/proteins (FXR, SHP-1, PPAR-α, CPT-1, MCAD and TGR5, FGF-21) was also rescued upon treatments. Finally, HFCD diet-induced overall mitochondrial dysfunction, as observed through the upregulation of DRP-1 and FIS-1 expression, concomitantly with downregulation of MFN2, OPA-1, NRF1, NRF2 and TFAM, was also inhibited by either INT-767 or antagomiR-21 alone, as well as both combined, at both timepoints
Conclusion: In conclusion, either INT-767 or antagomiR-21 alone prevent NAFLD triggering and progression, with both treatments combined more effectively ameliorating the NAFLD phenotype at distinct disease stages. These effects are mediated through modulation of multiple inflammatory-, fibrogenic-, insulin resistance-, mitochondrial function-, lipid and cholesterol metabolism-related genes, in overlapping and complementary signalling cascades. Hence, the multiple targeting of selected bile acid-activated receptors may embody a novel putative therapeutic approach in preventing NAFLD. SAICTPAC/0019/2015, PTDC/MED-PAT/31882/2017, EU H2020 Marie Sklodowska-Curie 722619.

FRI122
Patient-reported benefits for future non-alcoholic steatohepatitis therapy: a global real-world study among 1,035 patients across 12 countries

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Background and Aims: Non-alcoholic steatohepatitis (NASH) is estimated to increase 63% by 2030. Published evidence highlights a lack of patient understanding and long-term consequences linked to NASH. Health Technology Assessment (HTA) decisions, including UK-based National Institute for Health & Clinical Excellence (NICE), are increasingly requesting patient statement questionnaires around disease experience. This analysis aims to explore most important benefits patients seek from future NASH drug treatments.
Method: Data were derived from the 2018/19 Adelphi NASH Disease Specific Programme, a real-world, cross-sectional chart review in Europe (EU; France, Germany, Italy, Portugal, Spain, UK), North America (NA; US, Canada), Middle East (ME; Saudi Arabia, UAE), Australia (AU) & Japan (JP). Physicians completed questionnaires describing 2–8 NASH patients. Patients completed a voluntary questionnaire answering: Other than cure your fatty liver, what is the most important benefit your drug treatment could provide? 62 grouped responses generated 6 themes: diet and weight (DW), activities of daily living (ADL), feelings (F), reduce disease-related risks (RDR), treatment-specific benefits (TSB) and don't know (DK).
Results: 687 physicians (28% Hepatologist, 49% Gastroenterologist, 21% Diabetologist, 2% PCP) provided data on 3434 patients. Of these, 1035 patients (EU 600; NA 244; ME 102; AU 34; JP 55) provided a response, with 78 patients providing >1 response. Grouped responses reported DW 26%, ADL 17%, F 9%, RDR 17%, TSB 22% and DK 17%. NA patients were most concerned with DW (33% vs 9–26%) and RDR (26% vs 14–18%), AU/ME were most concerned with TSB (50% & 37% respectively vs 19–25%) and ADL (38% & 28% respectively vs 12–17%) and JP/EU most likely DK (25% & 24% respectively vs 5–7%). All $p < 0.05$. Minimal statistical differences across BMI, age, sex, disease duration, diagnostic tests, patient engagement/knowledge of disease.
Conclusion: Patient-reported expectations for NASH treatment benefits vary the most across regions suggesting cultural influence may drive expectations. However, lack of differentiation across other demographic, clinical and engagement factors could suggest a degree of homogeneity across NASH patients regarding treatment

expectations. This supports the notion that NASH patients, regardless of patient type, lack disease understanding and awareness supporting a need for enhanced patient education and engagement.

FRI123

Effects of kaempferol on CFLAR-JNK pathway in mice with non-alcoholic steatohepatitis

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Background and Aims: Non-alcoholic steatohepatitis (NASH), characterized by metabolic syndrome, hepatic steatosis, and liver inflammationmay, may progress to liver fibrosis, cirrhosis, and hepatocellular carcinoma. Without approved pharmacotherapy, the need to find appropriate therapeutic targets is more urgent than ever before. Recently, Fas-associated protein with death domain-like apoptosis regulator (CFLAR) has been proposed as a promising suppressor of steatohepatitis. Kaempferol (KAM), a natural flavonoid found in fruits and vegetables, has raised concern for its anti-oxidant, anti-inflammatory, and anti-apoptotic effects. The hepatoprotective effect of KAM has been indicated in drug-induced liver injury, alcoholic liver injury and acute liver failure, while its role against NASH remains unclear. The study aims to investigate the effect of KAM on CFLAR-JNK pathway and its downstream target genes concerning lipid metabolism, oxidative stress and inflammatory response in NASH models both *in vivo* and *in vitro*.
Method: *In vivo* study was performed on C57BL/6 male mice kept on a methionine/choline-deficient (MCD) diet or control methionine/choline-sufficient (MCS) diet from the age of 8 weeks to 12 weeks. Treatment with vehicle (0.5% carboxymethyl cellulose), KAM (50 mg/kg/d) was given for another 4–6 weeks via daily gavage (group size = 10). For *in vitro* study, oleic acid plus palmitic acid treated L02 cells were applied to establish the steatosis model. Key indicators involved in CFLAR-JNK pathway reflecting lipid metabolism, oxidative stress and hepatic injury were determined.
Results: Compared to the MCD models, treatment with KAM significantly improved the histological changes via decreasing parameters of steatosis, inflammation and fibrosis. CFLAR was activated while the pJNK was inhibited. KAM treatment could also improve the indicators as follows: (1) decreased the level of serum ALT, AST and TC, TG; (2) up-regulated hepatic transcript levels reflecting lipid metabolism, including *PPARα, FABP5, CPTLα, Acox, SCD-1, GPAT and MTTP* while suppressed lipid synthesis related genes including *SREBP-1c* and *PNPLA3*; (3) increased the level of NRF2 and the activities of oxygen radical scavenging enzymes (GSH-Px, CAT and HO-1) while reduced the expression of oxygen free radical generating enzymes (CYP2E1 and CYP4A). The regulation role of KAM in NASH was also confirmed by *in vitro* experiments.
Conclusion: Our results suggested that KAM can ameliorate NASH via activating CFLAR-JNK pathway. By targeting its downstream genes involved in the process of hepatic lipid synthesis (SREBP-1c, PNPLA3), β-oxidation (PPARα, FABP5, CPTLα, Acox) and transport (SCD-1, GPAT, MTTP) as well as hepatic oxidative stress (GSH-Px, CAT, HO-1, CYP2E1, CYP4A), KAM shows promising hepatoprotective property against NASH and may be a new therapeutic approach for NASH treatment.

Autoimmune and chronic cholestatic liver disease: Clinical aspects

FRI124

Serum gamma-glutamyltransferase is a prognostic biomarker in primary biliary cholangitis and improves risk stratification based on the alkaline phosphatase

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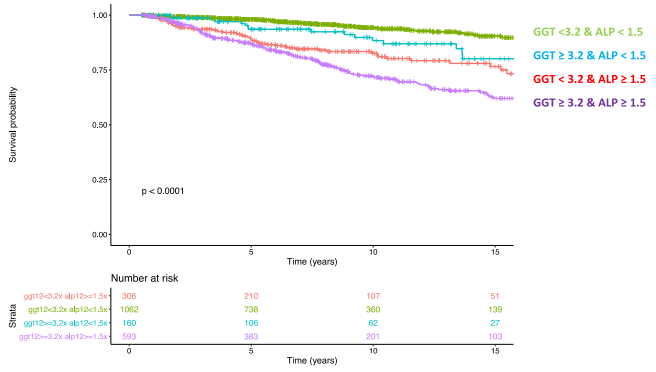
Background and Aims: Gamma-glutamyltransferase (GGT) is a serum marker of cholestasis. Its prognostic meaning in primary biliary cholangitis (PBC) is however unknown. We aimed to explore whether GGT is a prognostic marker in PBC.
Method: Data on patients from 14 centers from the Global PBC Study Group were included in the analysis. All patients with available GGT values at 12 months were selected. Levels of GGT were analyzed in different sub-populations at different time frames in relation to clinical endpoints of interest, i.e. liver transplantation (LT) or liver-related death.
Results: We identified 2129 patients, 281 (13%) experienced a liver-related clinical endpoint. Mean age at diagnosis was 53 years and 91% of patients were females. Patients treated with UDCA were 1983 (93%). Correlation between GGT and alkaline phosphatase (ALP) was strong (r = 0.71). When evaluated at baseline and yearly up to 5 years, higher GGT levels translated in lower transplant-free survival. When evaluated at 12 months since study enrollment, levels of GGT higher than 3.2 × upper limit of normal (ULN) best predicted the outcome at 10 years (AUC 0.70). The risk of liver-related death or LT in patients

with GGT higher than 3.2 × ULN despite ALP lower than 1.5 × ULN was higher compared to those with GGT lower than 3.2 × ULN and ALP lower than 1.5 × ULN (Figure). The GGT threshold of 3.2 × ULN confirmed its prognostic value in several subgroups, like young individuals (hazard ratio (HR) 3.52, confidence interval (CI) 2.15–5.77), male sex (HR 2.05, CI 1.06–3.96), and advanced histological stages (HR 2.53, 1.64–3.89). All findings were confirmed when patients not treated with UDCA were excluded. The trend of GGT/total bilirubin over time in patients who experienced LT or death decreased before the endpoint.



Conclusion: Serum GGT can predict liver transplantation or death of patients with PBC and enhances risk stratification based on ALP only. It might be used as surrogate end points in clinical trials. Moreover, GGT might replace ALP in patients with conditions that may spuriously alter levels of ALP, such as bone disease.

FRI125

Ursodeoxycholic acid and/or ciprofibrate for treating patients with presumptive diagnosis of low phospholipid cholelithiasis, a clinical spectrum of progressive familial intrahepatic cholestasis type 3

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Background and Aims: Low phospholipid-associated cholelithiasis (LPAC) is a clinical spectrum of progressive familial intrahepatic cholestasis type 3 (PFIC3) in which biliary phosphatidylcholine levels are reduced. Ursodeoxycholic acid (UDCA) is often effective. Fibrates may also be used theoretically due to their effects on peroxisome proliferator-activated alpha receptor activation, inducing bile secretion of phosphatidyl choline. The aim of the study was to retrospectively evaluate the safety and efficacy of fibrate in 29 patients (23 females) diagnosed with LPAC/PFIC3.
Methods: Diagnosis of PFIC3 was based on the detection of mutations in the ABCB4 gene. LPAC diagnosis was suggested by the presence of 2 of the following criteria: cholestasis in patients with cholelithiasis before age 40, recurrence of symptoms after cholecystectomy, intrahepatic lithiasis; cholelithiasis in first degree relatives; intrahepatic cholestasis of pregnancy or contraceptive-induced cholestasis. It was excluded other etiologies of chronic cholestasis. Liver enzymes and function and pruritus were analyzed after 3, 6 and 12 months of UDCA use and after ciprofibrate 100 mg/day by the Wilcoxon test; a p value <0.05 was considered statistically significant.
Results: Two patients (7%) were diagnosed with PFIC3 and 27 (93%) had clinical data compatible with LPAC. The mean age at onset of symptoms was 26.7 ± 13.6 years. Twenty-three patients (80%) had a family history of biliary diseases; 22 (76%) cholelithiasis before 40 years; 7 (24%) intrahepatic lithiasis. UDCA was given at a median dose of 13.4 mg/kg/day and ciprofibrate was added after a median time of 2.06 years of UDCA in 78% (22). During UDCA therapy, there was a significant decrease in aminotransferases, alkaline phosphatase and gamma-glutamyl transferase levels, without significant improvement in liver function. After addition of fibrate, pruritus resolved in all 7 patients, and there was improvement of the canalicular enzymes and albumin (only in the third month), with no significant worsening in renal function. Fibrate was stopped in 8 patients because liver transplantation (1), irregular use (2), side effects (5). The most common side effect was myalgia (2). Twenty-seven patients are in still in follow up.
Conclusion: Fibrate may be a safe and effective option to improve pruritus and laboratory tests in patients with LPAC/PFIC3 who were incompletely treated with UDCA. These findings should be confirmed by other centers.

FRI126

Comparative effects of second-line therapy with obeticholic acid or fibrates in primary biliary cholangitis patients

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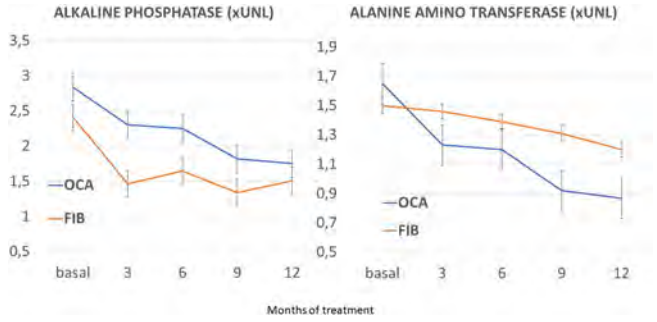
Background and Aims: Obeticholic acid (OCA) and fibrates are proposed as the second-line therapy in patients with primary biliary cholangitis (PBC) and suboptimal response to ursodeoxycholic acid (UDCA), but there is no definite data about their results in real life. Therefore, the aim has been to evaluate the comparative efficacy and adverse effects of OCA and fibrates.
Method: 355 patients (30 centres, Col-Hai registry) without optimal response to UDCA initiated therapy with fibrates, OCA or both. Biochemical changes during one year were analysed in patients

treated ≥ 3 months. Adverse effects and treatment discontinuation were recorded.
Results: 277 patients treated ≥ 3 months: 65 with OCA (5 mg/d), 201 with fibrates (84% bezafibrate 400 mg/d; 16% fenofibrate 200 -IQR 160–299- mg/d) and 11 with both OCA and fibrates. 90.9% women, 55 ± 1 year-old, 98.4% treated with UDCA for 7.5 ± 0.3 years, 11,8% with cirrhosis or portal hypertension and 13% with autoimmune hepatitis overlap. Baseline characteristics were similar between OCA and fibrates regimens, as well as in prognostic scores (UK-PBC and Globa-PBC). Both treatments decreased significatively alkaline phosphatase (AP), γ-glutamyl transferase (GGT) and transaminases. Fibrates improved the Global score (p = 0.01) and both treatments increased the percentage of patients with good prognosis according to this score. AP decrease was higher with fibrates (p = 0.002), while OCA has better on transaminases decrease (p = 0.05) (figure). Overlap syndrome (36% vs 9.2%, p < 0.01), and baseline hypertransaminasemia and biochemical cholestasis were higher in the 11 patients receiving OCA and fibrates concurrently. No significant changes were observed after 6 months of treatment in these patients.



Second-line treatment was discontinued in 9% of patients with OCA (2.2% no response; 2.2% intolerance) and 9.8% with fibrates (1.8% no response; 4% intolerance). Adverse events were reported in 10,1% with OCA and 3,6% with fibrates, mainly pruritus (3,5% with OCA). One patient with fibrates presented a severe adverse event.
Conclusion: Second-line therapy with obeticholic acid or fibrates improve hepatic biochemistry with infrequent adverse events in patients with primary biliary cholangitis non-responders to UDCA. Fibrates are associated with higher decrease in alkaline phosphatase while obeticholic acid with higher transaminases improvement.

FRI127

Histological features of non-alcoholic steatohepatitis are common in patients with autoimmune hepatitis who have advanced fibrosis at diagnosis

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Background and Aims: Given the growing prevalence of obesity and non-alcoholic fatty liver disease (NAFLD) it is likely that we will begin to see coincident NAFLD in patients with other liver conditions, such as autoimmune hepatitis (AIH). We aimed to evaluate the prevalence of histological features of non-alcoholic steatohepatitis (NASH) in patients presenting with AIH. We hypothesized that baseline fibrosis stage in patients with AIH is associated with histological features of NASH.
Method: We identified all adult patients who attended the liver clinic between 2013–2019 with a diagnosis of AIH. We used a cross-sectional design to analyse baseline characteristics of all patients including age, sex, body mass index (BMI), presence of type 2 diabetes (T2DM), hypertension and dyslipidaemia. We reviewed index biopsy reports for fibrosis stage, presence of steatosis, hepatocyte ballooning and lobular inflammation. We calculated odds ratios for the presence of histological features of NASH based on baseline fibrosis stage.
Results: 71 patients had a diagnosis of AIH and baseline biopsy data. 16/71 (22.5%) were male. Mean age (SD) was 60.7 years (16.3). 45/71 (63.4%) were overweight (BMI ≥ 25 kg/m^2) and 17/71 (23.9%) were obese (BMI ≥ 30 kg/m^2). At the time of diagnosis 7/71 (9.9%) had hypertension, 5/71 (7.0%) had T2DM and 4/71 (5.6%) had dyslipidaemia. 16/71 (22.5%) were cirrhotic at diagnosis. The prevalence of obesity was similar in patients with F3-F4 and F0-F2 fibrosis (25.0% vs 23.5%). Patients with F3-F4 fibrosis had an increased prevalence of steatosis (25.0% vs 15.7%), lobular inflammation (20.0% vs 0%) and ballooning (35.0% vs 5.5%), compared to patients with F0-F2. With F0-F2 as the reference, the crude odds ratio (OR) for presence of steatosis in F3-F4 was OR 1.8 [95% CI 0.51–6.3]). Crude OR for presence of ballooning in F3-F4 was OR 8.6 [95% CI 2.0–38.0]. Age adjusted OR for presence of ballooning in F3-F4 was aOR 1.75 [95% CI 0.11–27.6].
Table: Baseline characteristics in patients with AIH

	All patients with AIH n = 71		
Fibrosis stage at diagnosis	F0 – F2	F3 – F4	
Total number (%)	51 (71.8)	20 (28.2)	
Age (years) (± S.D.)	58.2 ± 17.7	67.0 ± 10.1	P < 0.05
Male sex (%)	12 (18.2)	4 (20.0)	
BMI (kg/m^2)	26.8 (23.4–30.2)	27.3 (25.0–31.0)	
Overweight ≥ 25 kg/m^2 (%)	30 (58.8)	15 (75.0)	
Obese ≥ 30 kg/m^2 (%)	12 (23.5)	5 (25.0)	
T2DM (%)	4 (7.8)	1 (5.0)	
Dyslipidaemia (%)	3 (5.9)	1 (5.0)	
Hypertension (%)	7 (13.7)	0 (0)	
Features of NASH on baseline biopsy			
Steatosis (%)	8 (15.7)	5 (25.0)	P = 0.361
Lobular inflammation (%)	0 (0)	4 (20.0)	P < 0.05
Ballooning (%)	3 (5.5)	7 (35.0)	P < 0.05

Conclusion: Obesity is encountered frequently in patients presenting with AIH. In patients with advanced fibrosis at diagnosis there is a high prevalence of histological features of NASH compared to patients without advanced fibrosis. However, after adjusting for age, fibrosis does not appear to be associated with a higher prevalence of histological features of NASH.

FRI128

Histological primary biliary cholangitis changes in patients with positive serology and normal alkaline phosphatase

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Background and Aims: The Swiss primary biliary cholangitis (PBC) cohort, established in 2017, includes also subjects with positive anti-mitochondrial antibody (AMA) and/or PBC-specific anti-nuclear antibody (ANA) and normal alkaline phosphatase (AP) serum

levels. We report the subgroup of subjects with isolated PBC-serology who have undergone a liver biopsy within one year of autoantibody testing.

Method: Preliminary report of the Swiss PBC cohort describing biochemical, serological and histological features of patients with isolated positive PBC-serology. Liver biochemistry was assessed before UDCA start in all patients.

Results: 66 patients with isolated PBC-serology have been included so far in the Swiss PBC cohort study, of whom 33 underwent a liver biopsy; six were excluded from data analysis for AIH-overlap, one for liver biopsy >1 year before serology test. 24 were female, median age 50 years, all Caucasian; 23 were AMA-positive, two were anti-centromere-positive, one ANA rim-like positive, confirmed by anti-gp210-positivity. PBC-compatible or -typical histological changes were seen in 22 patients, coexisting with NASH in one, the remainder showing steatosis (n = 2), NASH and normal histology (n = 1 each). Both subjects with isolated anti-centromere-positivity showed bile duct damage with granulomatous portal tract inflammatory infiltration (Figure). Two subjects had advanced fibrosis. While PBC histological changes were found in 16/17 (94%) of subjects with elevated GGT levels, only 6/9 (67%) subjects with normal GGT levels had PBC-compatible histology. Five subjects were on UDCA at the time of biopsy, median time on UDCA was two months.

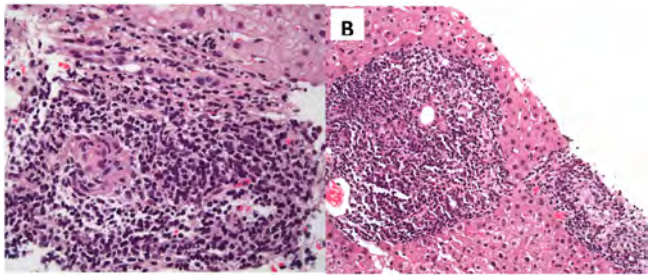

Figure: **A.** Liver histology of a 53-year old AMA-positive female patient with normal AP and GGT levels showing an epithelioid cell granulomatous reaction surrounding a bile duct (H&E 400x). **B**. Liver histology of a 44-year old AMA-negative, anti-centromere positive female patient with normal AP and normal GGT levels showing a portal tract with mixed chronic inflammatory cell infiltration surrounding a bile duct (H&E 200x).

Conclusion: these preliminary data not only confirm the frequent presence of PBC histological changes in patients with isolated AMA-positivity, but also demonstrate PBC-characteristic histology in patients with isolated anti-centromere antibody. Our data also suggest that GGT serum levels may be a novel disease marker in PBC.

FRI129

Ursodeoxycholic acid response in primary biliary cholangitis is associated with a significant reduction in decompensation and mortality in compensated cirrhosis

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Background and Aims: Most natural history studies of primary biliary cholangitis (PBC) have a relatively small number of patients with cirrhosis and little is known about the benefit of ursodeoxycholic acid (UDCA) in compensated cirrhotics. Therefore, the aim of this study is to compare UDCA responders and non-responders among PBC patients with compensated cirrhosis for the outcomes of hepatic decompensation and mortality (liver and non-liver related).

Method: This was a multicenter retrospective cohort study of 953 adult Veterans with PBC, diagnosed with compensated cirrhosis between 2008 and 2016 with follow up to June 2019. Entry date was defined as the first date of cirrhosis diagnosis. Patients who had decompensation at the time of cirrhosis diagnosis or follow-up of less than six months were excluded. UDCA was initiated at the time of PBC diagnosis and response was defined as alkaline phosphatase less than 1.67 times the upper limit of normal after one year of therapy. The associations of UDCA response and risk of decompensation and mortality were estimated using competing risk time-updating Cox proportional hazards models adjusted for age, sex, race-ethnicity, time-dependent AUDIT-C–defined alcohol use, diabetes, cirrhosis co-morbidity index, BMI, and Child Pugh score.

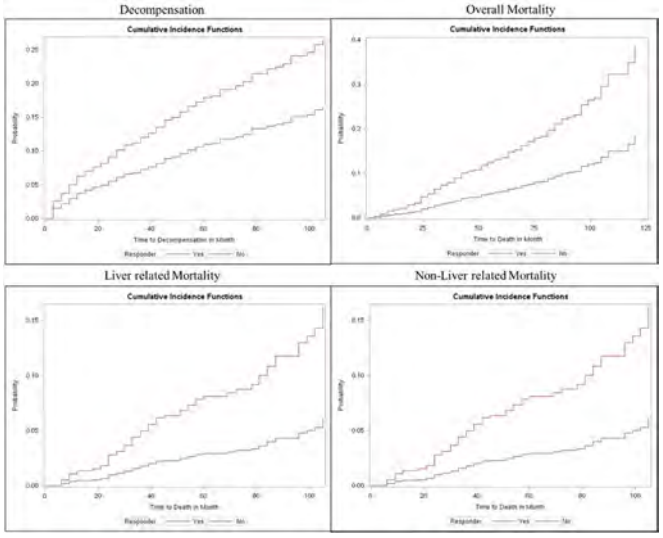

Figure: Cumulative Incidence of Decompensation, Death, Liver and Non-Liver related Death over Time, by UDCA response.

Results: A total of 953 patients with PBC and compensated cirrhosis with a follow-up of 4758 person-years were included in this study. Of these, 628 were UDCA responders. In comparison to non-responders, responders were less likely to develop decompensation (14% vs 21.9%, $p < 0.002$), including ascites (6.2% vs.13.5%, $p < 0.001$), encephalopathy (11.0% vs 12.9%, $p < 0.001$), variceal bleeding (11.0% vs. 12.9%, $p < 0.001$), and spontaneous bacterial peritonitis (1.6% vs 3.7%, $p < 0.001$). Further, responders were less likely to develop hepatocellular carcinoma (2.9% vs. 5.2%, $p < 0.001$). Responders also had significantly delayed median time to decompensation compared to non-responders (63 versus 49 months, $p < 0.002$). On adjusted multivariable analysis, UDCA response was associated with a 41% decrease in decompensation (HR 0.59, 95% CI 0.42–0.83), a 58% decrease of overall mortality (HR 0.42, 95% CI 0.29–0.61), a 65% decrease in liver-related mortality (HR 0.35, 95% CI 0.20–0.62), and a 54% decrease in non-liver related mortality (HR 0.46, 95% CI 0.27–0.77).

Conclusion: In a large cohort of patients with PBC and compensated cirrhosis, UDCA response is associated with a significant reduction in hazards of hepatic decompensation and mortality (liver and non-liver related).

FRI130

Male gender is associated with a high rate of decompensation and mortality in primary biliary cholangitis with well compensated cirrhosis

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Background and Aims: Most natural history studies of primary biliary cholangitis (PBC) have a relatively small number of male patients, particularly with cirrhosis. A recent study from the Global PBC study cohort of 4355 patients found that male gender was not associated with Ursodeoxycholic acid (UDCA) response or transplant free survival, but this cohort had only 59 males with portal hypertension at baseline. Other studies have shown that males have a delayed diagnosis and worse prognosis. The aim of this study was to identify the association of male gender with decompensation and mortality in a cohort of patients with PBC cirrhosis with a large proportion of males.
Method: This was a multicenter retrospective cohort study of 1167 Veterans with PBC who were diagnosed with compensated cirrhosis between 2008 and 2016 with follow up to June 2019. Cohort entry date was defined as the first date of cirrhosis diagnosis. Patients who had evidence of decompensation at the time of diagnosis of cirrhosis or who had a follow-up of less than six months were excluded. Response to UDCA was defined as alkaline phosphatase less than 1.67 times the upper limit of normal after 12 months of therapy. The associations of male gender and risk of decompensation, overall mortality as well as liver and non-liver related mortality were estimated using competing risk time-updating Cox proportional hazards models adjusted for age, sex, race–ethnicity, response to UDCA, and time-dependent AUDIT-C–defined alcohol use, diabetes, cirrhosis co-morbidity index, BMI and Child Pugh Score.

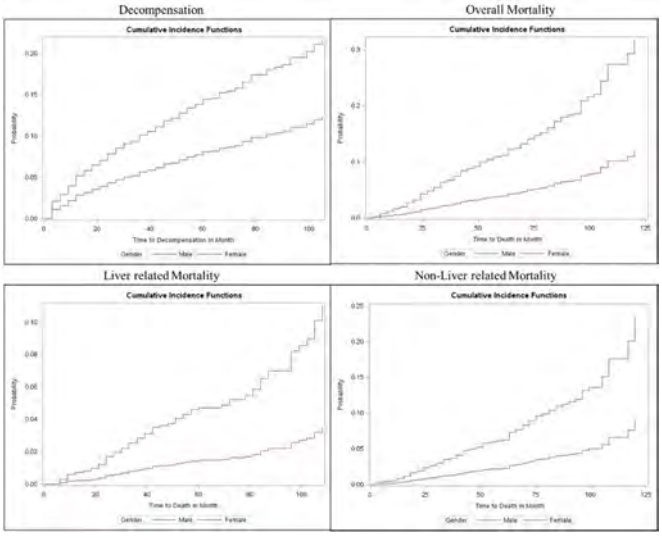

Figure: Cumulative Incidence of Decompensation, Death, Liver and Non-Liver related Death over Time, by Gender

Results: Of the 1167 patients with PBC, 924 were males. In comparison to women, men were older at diagnosis of cirrhosis (66.2 vs. 56.5 years, $p < 0.0001$), more likely to be white (71 vs. 65%), be diabetic (37 vs. 21%, $p < 0.0001$), and have an AUDIT score ≥ 4 at diagnosis of cirrhosis (7 vs. 3%, $p = 0.001$) and less likely to be UDCA responders (52 vs. 60%, $p = 0.04$). A total of 204 patients developed decompensation (19% of males vs. 10% of the females) with no significant difference in the median time to decompensation from diagnosis of cirrhosis (60 months in males vs. 62 months, $p = 0.12$). On adjusted Cox proportional hazard regression model, male gender was associated with higher hazard of decompensation (HR 1.85, 95% CI 1.16, 2.98), overall mortality (HR 2.98, 95% CI 5. 1.41–6.3), including liver (HR 3.26, 95% CI 1.13–9.45), and non-liver related mortality (HR 2.85, 95% CI 1.00–8.11).
Conclusion: In this large cohort of patients with PBC and compensated cirrhosis with a predominant male population, male gender was associated with a significant increase in hazards of hepatic decompensation and mortality.

FRI131

Psychometric evaluation of the adult itch reported outcome tool, a worst-itch numeric rating scale in adults with cholestatic liver disease

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Background and Aims: Cholestasis often leads to severe pruritus, which may significantly impair quality of life. The Adult Itch Reported Outcome (ItchRO) is a single-item, numeric rating scale (NRS) measure that assesses the severity of pruritus with an 11-point scale (0 = no itch to 10 = worst possible itch). The measure was originally developed using qualitative methods and cognitive debriefing with primary biliary cholangitis (PBC) patients. This study aimed to validate the Adult ItchRO for pruritus in adult patients with either primary sclerosing cholangitis (PSC) or PBC.
Method: During two clinical studies of the apical sodium-dependent bile acid transporter (ASBT) inhibitor maralixibat: a 13-week randomized double-blind, placebo-controlled study in PBC and a 14-week pilot open-label study in PSC patients, the Adult ItchRO was completed twice daily (morning [AM] and evening [PM]) along with other co-validating measures. Analyses for the exchangeability of the AM and PM ratings were used to establish a score. Scores were examined for reliability and validity. A patient impression of change (PIC) was completed by the PBC study patients and used to establish the minimal clinically important change (MCIC) of the Adult ItchRO. To accommodate different designs, analyses were conducted within both trials.
Results: Data from 61 PBC and 27 PSC patients were eligible for analysis. No differences were observed in patients' AM and PM ratings of the Adult ItchRO, thus a weekly average score of the daily worst itch rating was calculated to align with other NRS. Test retest reliability estimates using a one-week lag and the two-way random intra-class correlation coefficient were 0.93 and 0.98. Convergent validity of the scores in both studies was established with the 5D-Itch Total Score ($r = 0.59$ to 0.95) and PBC-40 Itch domain ($r = 0.51$ to 0.85). The distribution-based analysis of the PBC study to establish a change score that reflected true underlying change in pruritus showed that the MCIC = –1.86. The anchor-based analysis of the PBC study using the PIC showed that the average scores between those rating "No change" versus "A little better" showed that the MCIC = –1.86.
Conclusion: Results from the present analyses demonstrate that the Adult ItchRO is a reliable and valid measure able to detect small changes in pruritus, which are clinically meaningful in patients with cholestatic liver diseases.

FRI132

Effectiveness of obeticholic acid (OCA) in southern European patients with primary biliary cholangitis (PBC) as a second line therapy. A multicenter, international, real- world cohort

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Background and Aims: Obeticholic Acid (OCA), a potent farnesoid X receptor agonist was recently approved for patients with primary biliary cholangitis (PBC) and suboptimal response/intolerance to ursodeoxycholic acid (UDCA). There is limited information on the OCA effectiveness and safety in the real practice setting. Here we present a real world cohort of PBC patients with incomplete response to UDCA therapy. The primary outcomes were the rate of patients achieving response (Paris-2 criteria) and reduction in GLOBE and UK-PBC scores from baseline. Secondary outcome was the OCA effect in non-invasive fibrosis score aspartate transaminase to platelets ratio index score (APRI).

Method: Open-label real practice multicenter study from 19 centers from Spain and Portugal, to assess OCA effectiveness and safety in patients with inadequate response to UDCA (Paris 2 criteria). Data are presented are mean ± standard deviation or median (interquartile range).

Results: One hundred and two patients were included, age 57.1 ± 10.8, females (94.1%), time since PBC diagnosis 11 ± 6.8 yrs., 81 and 59 were AMA and ANA positive (79.4% and 57.8%), respectively. The median F-U: 7.2 months. (IQR: 4.4–12.5). Thirty five patients completed 1 year of OCA treatment (34.3%), alkaline phosphatase (AP) decreased from 273 (IQR: 209–388) to 203 (IQR: 178–266) IU/L ($p < 0.001$), ALT decreased from 42 (IQR: 25–63) to 26 (IQR: 21–38) IU/L ($p < 0.001$). Twenty percent of patients achieved optimal response (Paris 2 criteria), with an alkaline phosphatase decrease of 30%. However, alkaline phosphatase also decreased a 20% in incomplete responders (Figure). APRI score improved from 0.58 (IQR: 0.41–1.01) to 0.49 (IQR: 0.36–0.82) ($p = 0.005$). The UK PBC score improved at 5, 10 and 15 years, from 1.7 (IQR:1.1–4.4), 5.6 (IQR:3.5–14) and 10.1 (IQR:6.4–24.5) to 1.8 (IQR:0.8–3.5), 5.9 (IQR:2.5–11.2) and 10.7 (IQR:4.6–19.7). respectively ($p < 0.01$). However, the GLOBE-PBC score reduction did not reach significance ($p = 0.14$). During OCA treatment, 34.3% developed adverse effects and six patients discontinued OCA treatment (5.9%). At univariate analysis, older age 63 (IQR: 59–69) vs.53 yrs. (IQR: 43–63); $p = 0.03$, lower baseline serum AP 210 (IQR: 163–296) vs. 289 (IQR: 227–454) IU/mL and bilirubin 0.5 (IQR: 0.32–0.52) vs. 0.82 (IQR: 0.5–1.45) mg/dL were associated to complete response (Paris 2 criteria).

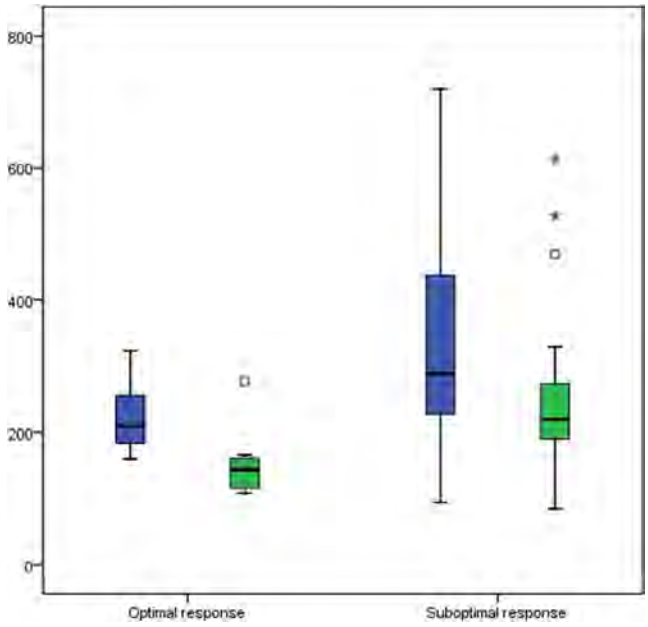

Figure: Values of serum Alkaline Phosphatase in responders and non-responders (Paris-2 criteria) the decrease of AP was a 31% from baseline in responders and a 20% in incomplete responders.

Conclusion: OCA treatment significantly improved the UK-PBC and APRI Scores. In addition, this drug increased the rate of patients who achieved Paris-2 complete response, older age and lower baseline serum bilirubin and AP were significantly associated to complete response. The rate of OCA discontinuation due to adverse effects was low.

FRI133

Durability of treatment response after 1 year of therapy with seladelpar in patients with primary biliary cholangitis (PBC): final results of an international phase 2 study

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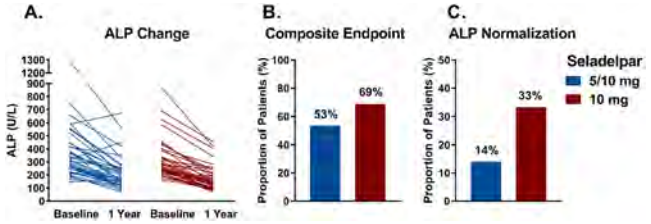
Background and Aims: Seladelpar is a potent and selective peroxisome proliferator activated receptor-delta agonist that has shown improvement in markers of cholestasis in PBC patients. We evaluated the efficacy, safety, and tolerability of seladelpar during 1 year of treatment in patients with PBC.

Method: This was a 1-year, Phase 2, open label uncontrolled dose-finding study in PBC patients with an inadequate response or intolerance to ursodeoxycholic acid (UDCA). Eligible patients had alkaline phosphatase (ALP) ≥ 1.67 × ULN, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 ULN and total bilirubin (TB) ≤ 2 mg/dL. Patients received oral daily doses of 2, 5 or 10 mg seladelpar; after 12 weeks, doses could be increased up to 10 mg based on biochemical response. The primary endpoint was percent change in ALP. After 1 year, patients were offered a long-term study.

Results: Of 119 PBC patients treated with seladelpar, 112 were evaluated for efficacy [2 mg (N = 11), 5 mg (N = 49) and 10 mg (N = 52)]. At 1 year, no patients remained on 2 mg and no results are presented for this group.

Patients were predominantly female (95.5%), with a mean age of 57.5 ± 9 years, mean duration of PBC 10 ± 7 years, and mean UDCA dose of 15 ± 4 mg/kg/day. Mean baseline values in the 5/10 mg and 10 mg dosage groups were: ALP 353 U/L and 301 U/L, TB 0.76 mg/dL and 0.83 mg/dL, GGT 244 U/L and 239 U/L, and ALT 46 U/L and 46 U/L. After 1 year of treatment, nearly all patients decreased ALP (Figure 1A) with mean decreases of 40% in 5/10 mg and 45% in 10 mg groups. The composite endpoint (ALP < 1.67 × ULN and −15% and TB < ULN) was met in 53% patients in 5/10 mg and 69% in 10 mg (Figure 1B). 14% of patients in 5/10 mg and 33% in 10 mg normalized ALP (Figure 1C). TB was stable over the year. GGT decreased by −34% in 5/10 and −32% in 10 mg. ALT decreased by 31% in both groups. Over 1 year, seladelpar appeared safe, well tolerated, and did not induce pruritus. 14 patients experienced SAEs, all unrelated to the drug. 4 patients discontinued seladelpar due to adverse events, 2 were considered related to the drug (heartburn, Grade 1 and ALT/AST elevation, Grade 2). 98% (104) of eligible patients enrolled in the long-term follow-up study.



Conclusion: In patients with PBC treated for 1 year, seladelpar resulted in a substantial and sustained biochemical response with a good tolerability and safety profile. Seladelpar is being further evaluated in PBC in the Phase 3 ENHANCE study.

FRI134

Hepatocellular carcinoma in patients with autoimmune hepatitis: prevalence and risk factors

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Background and Aims: The prevalence and risks factors for hepatocellular carcinoma (HCC) occurrence in autoimmune hepatitis (AIH) are unclear. The aims of this study were to describe HCC prevalence in AIH in a tertiary referral hospital as well as clinical, laboratorial and radiological features and treatment outcomes.

Method: Retrospective cohort of AIH patients followed from 2003 to 2019. HCC-free survival was defined as the time interval between AIH and HCC diagnosis or the end of follow up. The hazard ratios (HR) and their respective 95% confidence intervals (CIs) were estimated using the simple Cox regression. A multivariate regression model was fitted using relevant covariates for HCC occurrence. P values < 0.05 were considered significant.

Results: 355 patients, 84.5% female, 85% AIH-1, mean age at diagnosis of AIH 27 ± 18 years, 65% with cirrhosis. Sixteen cases of HCC were diagnosed (4.5%), all of them in cirrhotic patients, 81.3% female, mean age of 49 ± 20 years, 83% overweight (mean BMI 34 ± 5 kg/m^2) and 3 with steatohepatitis. The pooled incidence rate for HCC in patients with AIH was 3.2 per 100 patient-years. The pooled incidence of HCC in patients with cirrhosis at AIH diagnosis was 4.5 per 100 patient-years. The median time between AIH diagnosis and HCC was 9 years (1-42). At univariate analysis the factors associated with HCC risk were age at diagnosis of AIH, platelet count <100 × 10^6/mm^3 (HR,4.77; 95%CI, 1.73–13.17;p = 0.003), presence of portal hypertension at diagnosis, diabetes (HR,3.89; 95%CI, 1.18–12.7;p = 0.025) and disease remission at any time of follow up. At multivariate analysis the factors associated with HCC risk were age at diagnosis (HR,1.05; 95%CI, 1.027–1.083;p < 0.001) and portal hypertension at diagnosis (HR,4.88; 95%CI, 1.49–15.92;p = 0.009). The occurrence of disease remission during follow up was associated with lower risk of HCC occurrence (HR,0.128; 95%CI, 0.043–0.38;p < 0.001). At diagnosis of HCC 62.5% were unique, mean diameter of the largest lesion of 3.5 cm, 50% BCLC 0-A, 37.5% BCLC B and 12.5% BCLC C. Survival at 1 year was 43.7% and at 5 years 6%.

Conclusion: The prevalence of HCC in this cohort was 4.5%. Advanced age at diagnosis, diabetes, platelet count <100 × 10^6/mm^3, presence of portal hypertension at diagnosis and absence of disease remission during treatment were associated with greater risk of HCC. Our study

have the limitations of a retrospective analysis and our findings should be confirmed in other populations.

FRI135

Safety, tolerability, pharmacokinetics and pharmacodynamics of a novel farnesoid x receptor (FXR)-TQA3526 in healthy Chinese volunteers: a double-blind, randomized, placebo-controlled, dose-escalation, food effect phase? study

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Background and Aims: TQA3526, a novel farnesoid X receptor (FXR)-selective high affinity agonist. The concentration for 50% of maximal effect of TQA3526 for FXR cytoactive is 100 times higher than that of OCA in vitro (3.1 VS 385.0 nM). This Phase I first-in-human study was designed to evaluate the safety, tolerability, PK and PD of TQA3526 in healthy volunteers.

Method: Healthy volunteers aged 18–55 years were enrolled in this study. Part 1 and part 2 were single ascending dose (SAD) (1 mg 2 mg 5 mg and 10 mg) and multiple ascending dose (MAD) (0.2 mg 0.5 mg 1 mg for 10 consecutive days in a titration way) under fasted conditions, and part 3 was a food effect study (10 mg) with 10 days washout period.

Results: TQA3526 was well tolerated in 1 mg 2 mg 5 mg 10 mg fasted SAD group and 0.2 mg 0.5 mg 1 mg MAD group, the most common treatment emergent adverse events (TEAEs) was pruritus, liver ingury and abdominal disorders, which were expected based on its mechanism, and showed a dose-related trend. Fed conditions showed less tolerance compared with fasted conditions.

AUC0-∞ (158.9–2490 h*ng/ml) and Cmax (10.925–120 ng/ml) exhibited a linear increase. Plasma TQA3526 concentrations peaked 2 to 5 hours postdose, median t1/2 ranged from 8.93–16.69 hours, supported QD dosing. The fed group AUC0-∞ (2600.47 h*ng/ml) increased almost 43% compared to the fasted group AUC0-∞ (1817.78 h*ng/ml). Accumulation of TQA3526 was low with accumulation ratios (RAUC) of 1.4. In the MAD study, steady-state conditions were achieved after 5 days of daily dosing.

C4 levels reduced approximately 90% in 24 hours in 1 mg TQA3526 SAD and showed a proportional linear decrease. The MAD result of C4 haven't came out. FGF19 levels increased approximately 2.5-fold in 0.5 mg TQA3526 MAD versus 8.3% 2 degree pruritus, and increased approximately 5-fold in 1 mg TQA3526 MAD versus 33.3% 3 degree pruritus.

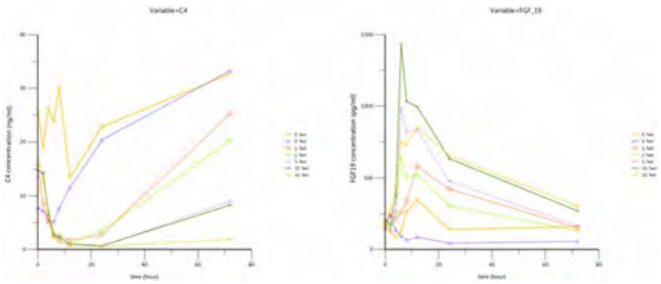

Figure: mean C4 (ng/ml) and FGF19 (pg/ml) plasma concentration-time profiles for the SAD.

Conclusion: TQA3526 was well tolerated at single dose up to 10 mg/d, multiple dose up to 1 mg/d, with a linear pharmacokinetic and pharmacodynamics profile among all subjects, which proved efficient since 0.5 mg.

FRI136

Temporal trends of autoimmune hepatitis related hospitalizations: a descriptive study

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Background and Aims: Autoimmune hepatitis (AIH) is caused by circulating autoantibodies that result in chronic, inflammatory disease of the liver, which manifests as acute hepatitis and progresses to chronic liver disease and cirrhosis. Our study aims to perform a nationwide survey of the hospitalization trends for AIH through large database analysis.

Method: The National Inpatient Sample (NIS) is the US largest publicly available database to analyze different hospital-related outcomes. We queried NIS from 2008 to 2014 to identify all the hospitalization related to AIH identified with ICD-9 CM code "571.42" as a primary diagnosis and secondary diagnosis. Our primary outcome of interest was to measure the yearly hospitalization rate associated with AIH as a primary and secondary diagnosis. Secondary outcomes included inpatient mortality, length of stay (LOS), inflation-adjusted total hospitalization charges, and complications associated with AIH related hospitalizations such as acute liver failure, acute kidney injury, portal hypertension, need for mechanical ventilation, liver biopsy, and liver transplant.

Results: A total of 11,621 and 78,165 nonelective hospitalizations for adults age above 18 years were recorded between 2008 and 2014 for AIH as a primary diagnosis and secondary diagnosis, respectively. The outcomes were analyzed separately for primary and secondary diagnoses. The prevalence of hospitalizations for AIH increased significantly over the years, from 0.19 to 0.91 for primary diagnosis, and from 1.08 to 5.68 for secondary diagnosis group per 100,000 patients. Mean age was recorded 50 years for primary AIH and 57 in secondary AIH, with the majority comprising of females (81%) in both the groups. A total of 513 (4.41%) patients in the primary and 3,144 (4.02%) in the secondary group died within the same admission. Mean LOS was recorded 6.7 in the primary vs. 5.7 days in the secondary group. Mean total hospitalization charges were found to be higher in the primary group 62,729$ vs. 49,886$). Comparison of major complications in these two groups is as follows, acute kidney injury 1,241 (10.67%) vs. 10,832 (13.85%); acute liver failure 778 (6.69%) vs. 2,180 (2.79%); portal hypertension 2,009 (17.2%) vs. 11,927 (15.25%); mechanical ventilation, 417 (3.5%) vs. 3,470 (4.43%); liver biopsy 3,963 (34.10%) vs. 3,838 (4.9%); liver transplant 394 (3.33%) vs. 476 (0.6%) underwent liver biopsies and liver transplant respectively in the primary AIH group.

Figure: Temporal Trends of AIH related hospitalization rate as a primary and secondary diagnosis

Conclusion: Our study showed that the hospitalization rate of AIH as a primary as well as the secondary diagnosis is on the rise. This can be explained either by improved diagnostic techniques or a real increase in the autoimmune disorders in the general population, which needs to be further evaluated through large prospective cohort studies.

FRI137

Ursodeoxycholic acid reduces cholestatic hepatitis and maternal bile acid levels in intrahepatic cholestasis of pregnancy

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Background and Aims: Intrahepatic cholestasis of pregnancy (ICP) is the commonest pregnancy-related liver disorder, characterized by pruritus without rash and increased serum bile acids (BA) >10 mmol/L. We reviewed the management and outcomes of patients with ICP over a period of 1 year when managed with UDCA.

Table: Maternal characteristics of women with ICP n = 375.

Variable	Entire Cohort (n = 375)	Mild ICP (n = 341)	Severe ICP (n = 34)	Gestational Pruritus (n = 68)*
Maternal Age (years, median/IQR)	26.7 (21.3–33.6)	26.5 (21.6–32.4)	27.4 (22.1–34.3)	26.9 (21.2–32.1)
Gestational age at presentation (weeks)	32 (24–34)	32 (31–35)	26 (24–30)†	29 (25–31)
Prior ICP	161 (42.9%)	143 (41.9%)	18 (26.4%)†	0
Maternal history of ICP	45 (12%)	29 (8.5%)	16 (47%)†	0
Highest bile acid concentration mmol/L (median, IQR)	25 (18–34)	18 (14–29)	98 (49–85)†	5 (2–8)
Medication Usage				
UDCA	375 (100%)	341 (100%)	34 (100%)	54 (79.4%)
Cholestyramine	14 (3.7%)	4 (1.1%)	10 (29.4%)	0
Dexamethasone	33 (8.8%)	24 (7.0%)	9 (26.4%)†	0
Onset of Labour				
Spontaneous	347 (92.5%)	319 (93.5%)	28 (82.3%)	56 (82.3%)
Induced Labour	28 (7.5%)	22 (6.4%)	6 (17.6%)†	12 (17.6%)
Mode of Delivery				
Vaginal	289 (77.0%)	267 (78.2%)	24 (74.8%)	64 (94.1%)
Caesarian section	86 (22.9%)	74	12 (35.2%)†	4 (5.9%)
Neonatal Outcome				
Neonatal Distress	31 (8.2%)	16 (4.6%)	15 (44.1%)†	6 (8.8%)
Still Birth	8 (2.4%)	5 (1.4%)	3 (8.8%)†	0

Abbreviations: IQR, interquartile range, ICP, intrahepatic cholestasis of pregnancy.
†p < 0.05 when mild ICP is compared with severe ICP.

Method: All pregnancies associated with ICP (defined as pruritus with serum bile acids) were prospectively included with analysis of demographics, maternal/perinatal outcomes co-morbidities and treatment response. Mild and severe ICP were diagnosed when serum BA was always <40 mmol/L, and ≥ 40 mmol/L respectively. Patients with gestational pruritus were taken as controls.

Results: Of 643 screened pregnant women, 375(mean age 29 years; 45.8% primigravida) of these patients met diagnostic criteria for ICP. In ICP, incidences of pregnancy induced hypertension (PIH; 10.3%; OR4.8, 95%CI 2.6–9.7, P = 0.043), gestational diabetes (12.5%; OR2.6, 95%CI 2.3–4.1, P = 0.029), and spontaneous preterm labour (15.1%; OR1.8, 95%CI 1.3–2.9, P = 0.034) were higher than in the general pregnant population. Response to UDCA (median daily dose 900 mg; 600–1800 mg) was seen in 79% patients with resolution of pruritus and normalization of liver enzymes. Patients with severe ICP (serum BA>40 mmol/L) presented earlier (26 vs. 32 weeks, P = 0.036), required induction (12%; OR2.1 95%CI 1.8–4.3, p = 0.045) with increased foetal distress than those with mild ICP. (Figure). There were 8 stillbirths.

Conclusion: Our study showed safe maternal outcomes with mild ICP but with persistent risk for stillbirths, pre-term labour, and need for induction in severe ICP. UDCA ameliorated symptoms of cholestasis in 79% patients.

FRI138

Poor diagnostic accuracy of blood igG4/igG RNA ratio for discriminating igG4-related disease from pancreatic or biliary cancer (DIPAC): a prospective cohort study

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Background and Aims: IgG4-related disease (IgG4-RD) of the pancreas and biliary tract is difficult to distinguish from pancreato-biliary cancer. Misdiagnosis may result in unnecessary major surgical interventions or chemotherapy. The blood IgG4/IgG RNA ratio determined by quantitative polymerase chain reaction (qPCR) was reported by us to discriminate IgG4-RD from PSC or biliary and pancreatic cancer with high accuracy[1]. This study aimed to assess prospectively the diagnostic accuracy of blood IgG4/IgG RNA ratio for the differentiation between IgG4-RD and cancer in a cohort of patients with suspicion of pancreatobiliary malignancy.

Method: In this prospective, observational study, all patients presenting at a specialized hepato-pancreato-biliary clinic with suspicion of pancreatobiliary malignancy were included between February and August 2019. The IgG4/IgG RNA ratio was determined in addition to standard diagnostic procedures (threshold 5.0%[1]). In all patients, clinical and laboratory data were collected. Histo- or cytopathological findings were analyzed in patients who underwent a biopsy, brush or surgery of the pancreas or biliary tract and liver. For the diagnosis of IgG4-RD, the HISORt criteria were used as reference standard. Malignancy was defined by the presence of neoplastic cells at histo- or cytopathological examination.

Results: In this interim analysis, 213 consecutive patients were investigated of whom 104 (48.8%) were male and 109 (51.2%) were female with an age of 68 ± 11 years. Three patients were diagnosed with IgG4-RD, in two of these, serum IgG4 was markedly elevated (>14.0 g/L; upper limit of normal 1.4). 175 patients were diagnosed with a malignancy of whom 163 patients with malignant disease of the pancreas or biliary tract (108 pancreatic cancer, 37 cholangio-carcinoma, 11 carcinoma of the papilla of Vater, 7 gallbladder carcinoma). In 3 patients (1.6%), the qPCR test was true positive and in 87 (40.7%) false positive. In 123 (57.5%) patients the test was true negative. The sensitivity of the IgG4/IgG RNA qPCR was 100%, the specificity 59%, the positive predictive 3.3%.

Conclusion: An elevated IgG4/IgG RNA ratio did not accurately discriminate pancreatic and biliary cancer from IgG4-RD as illustrated by low specificity and concordant low positive predictive value. We decided to stop the trial and advise against the use of this test for discrimination of IgG4-RD from pancreatic and biliary malignancies outside a research setting.

Reference

1. Doorenspleet ME, Hubers LM, Culver EL, et al. Immunoglobulin G4(+) B-cell receptor clones distinguish immunoglobulin G 4-related disease from primary sclerosing cholangitis and biliary/pancreatic malignancies. *Hepatology* 2016;64:501–7.

†p < 0.05 when mild ICP is compared with severe ICP.

FRI139

Glucuronidation directs systemically available norursodeoxcholic acid (norUDCA) to the kidney

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Background and Aims: *Nor*UDCA is a chemically modified bile acid with clinically proven therapeutic potential in cholestatic and metabolic liver diseases. Due to shortening of the side chain, *nor*UDCA is evading the natural bile acid metabolism resulting in a unique pharmacokinetic profile.
Method: Six healthy male volunteers were treated with a single oral dose of 1500 mg [14C]-labelled *nor*UDCA. Plasma pharmacokinetics and excretion of radioactivity in urine and faeces were followed over a period of 264 h. Metabolites found in plasma, faeces and urine were identified and quantified by a combination of radio-chromatography and liquid chromatography with tandem mass spectrometry (LC-MS/MS).
Results: Following oral administration of [14C]-*nor*UDCA, 64% of the radioactivity was excreted with the urine while approximately 30% was recovered from the faeces. *Nor*UDCA accounted for 56% of the circulating plasma total radioactivity and showed maximal plasma concentrations of 37 µg/mL at a Tmax of 4 h and an elimination half-life of 27 h. NorUDCA-23-acylglucuronide (*nor*UDCA-AG) was the main metabolite of norUDCA in plasma and demonstrated similar pharmacokinetics as its parent compound *nor*UDCA. Other metabolites found in plasma resulted from isomerisation of *nor*UDCA and from a combination of glucuronidation and sulfation. The main drug-related compound found in urine was *nor*UDCA-AG, while fecal samples contained mainly unchanged *nor*UDCA.
Conclusion: *Nor*UDCA is absorbed with a high oral bioavailability resulting in a relatively high systemic exposure in plasma. The study demonstrates predominant *nor*UDCA glucuronidation with subsequent urinary elimination. The high systemic exposure suggests that *nor*UDCA could have extrahepatic effects, in particular in the kidney. This could be of potential clinical relevance for jaundiced patients with cholemic nephropathy, in line with pre-clinical evidence (Norursodeoxycholic acid ameliorates cholemic nephropathy in bile duct ligated mice, Krones et al. *J Hepatol* 2017; 67(1):110–119).

FRI140

Predictive factors of response to corticosteroid therapy in acute severe autoinmune hepatitis: a national multicentric study

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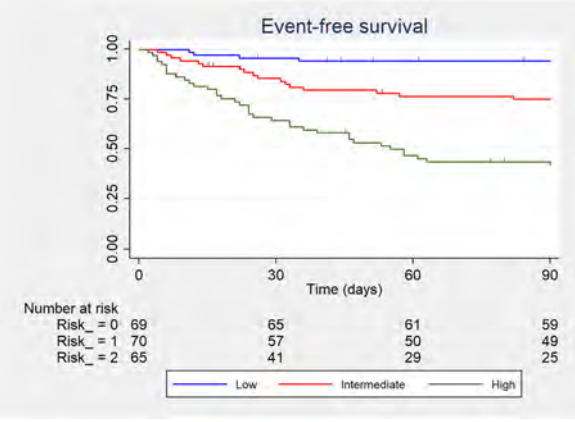
Background and Aims: Acute severe autoimmune hepatitis (AS-AIH) is a disease poorly characterized, with weak evidence-based criteria to guide diagnosis and treatment. The usefulness of corticosteroids in this setting as well as the predictors of response to these drugs remain controversial. In consequence, AS-AIH represents a challenge for liver transplant (LT) clinicians. Aim: To identify predictive factors of response to corticosteroids in patients with AS-AIH.
Method: Multicenter and retrospective study including patients with AS-AIH, defined as an acute presentation of AIH with INR ≥ 1.5 at any time, between 01/01/2002–31/12/2018 at 13 tertiary centers in Spain. A multivariable survival analysis using Cox´s regression model was performed to identify those variables associated with a poor outcome (90 day -overall and -transplant-free survival) and a predictive model was developed to predict response to corticosteroids.
Results: (mean ± SD). 242 consecutive patients were enrolled (female 74,4%), mean age 49,68 ± 16,81 years. 90 days -overall and -transplant-free survival rate was 62,8%. Corticosteroid therapy was significantly associated with a better outcome (adjusted HR: 0.18, IC 95%: 0.11–0.29%). This treatment failed in 59/205 (28.8%) patients (90-day mortality: 15.1%; LT: 15.6%). Factors associated with treatment failure were age, MELD, presence of ascites and hepatic encephalopathy. Based on these data, a **predictive model** was developed: age in years*0.02 points + MELD >25 (1 point) + ascites (0,5 points) + hepatic encephalopathy (EH, 0,25 points). Obtaining <1 point predicted a high probability of response to steroids (90 day – overall and transplant-free survival was 88%), whereas >1.7 points implied a low probability of response (figure 1).



Conclusion: Corticosteroids are a useful treatment for patients with AS-AIH. Older age, MELD and the presence of ascites and hepatic encephalopathy are early predictors of poor response to corticosteroids.

FRI141

Antibodies against glycoprotein 2 and anti-neutrophil cytoplasmic antibodies targeting the serine proteinase 3 are markers of severe primary sclerosing cholangitis (PSC) and progression to cholangiocarcinoma (CCA)

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Background and Aims: Anti-glycoprotein 2 (anti-GP2, also called anti-MZGP2) and anti-neutrophil cytoplasmic antibodies to serine proteinase 3 (PR3 ANCA) have been linked with inflammatory bowel disease and PSC. In PSC, anti-GP2 IgA has been suggested as a marker of disease severity and poor outcome related to CCA and PR3 ANCA as a marker of disease severity. In this study we assessed the value of anti-GP2 IgA and PR3 ANCA as predictors of progressive disease course and poor outcome in a large cohort of PSC patients.
Method: 338 patients with PSC (age range 17–73, 65% male, 26% cirrhotic, 3.8% developed CCA during follow-up) were prospectively evaluated. Anti-GP2 IgA (isoforms 1 and 4) were detected by ELISAs (GA Generic Assays, Germany) and PR3 ANCA by chemiluminescence immunoassay (Inova Diagnostics, San Diego; using optimized cut-off of 10 units). Poor disease outcome was defined as liver transplantation and/or liver-related death during a median follow-up of 14 months.

	Anti-$GP2_1$ IgA			Anti-$GP2_4$ IgA			PR3 ANCA		
Feature (median)	Neg	Pos	p	Neg	Pos	p	Neg	Pos	p
PLT (ths/ul)	256	209	**0.007**	247	210	NS	229	255	NS
BIL (mg/dl)	0.9	1.6	**<0.001**	0.9	1.7	**0.02**	0.8	1.1	**0.02**
ALP (IU/L)	216	317	**<0.001**	242	225	NS	197	294	**<0.001**
GGT (IU/L)	197	200	NS	204	140	**0.02**	150	213	**0.005**
ALT (IU/L)	76	81	NS	79	68	NS	65	87	**0.007**
AST (IU/L)	57	77	**0.03**	63	62	NS	55	70	**0.003**
ALB (g/dl)	4.2	3.9	**<0.001**	4.2	4.0	**0.001**	4.2	4.1	NS
INR	1.0	1.1	**<0.001**	1.0	1.1	**0.005**	1.0	1.1	**0.01**

Results: Anti-$GP2_1$ IgA occurred in 79 (23%), anti-$GP2_4$ IgA in 58 (17%), and anti-$GP2_1$ and/or anti-$GP2_4$ IgA in 103 (30%) patients. PR3 ANCA positivity rate was 54.5%. Anti-GP2 IgA and PR3 ANCA were associated with poor liver function (Tab. 1). Cirrhosis was associated with anti-$GP2_4$ IgA ($p = 0.003$). CCA occurred more often in patients with anti-$GP2_1$ IgA ($p = 0.04$) and PR3 ANCA ($p = 0.008$). 100% of CCA patients were positive for PR3 and/or anti-GP2 IgA. Significant associations between anti-$GP2_1$ IgA, anti-$GP2_4$ IgA, PR3 ANCA and poor outcome were found ($Chi^2 = 11.2$, HR = 2.1, 95%CI = 1.4–4.2, $p = 0.0008$; $Chi^2 = 7.8$, HR = 2.4, 95%CI = 1.3–4.5, $p = 0.005$; $Chi^2 = 6.87$, HR = 1.8, 95%CI = 1.2–2.8, $p = 0.009$; respectively). Cox proportional-hazards regression indicated anti-$GP2_1$ IgA and lower albumin level as independent variables of poor outcome ($p < 0.0001$), while anti-$GP2_4$ IgA and PR3 ANCA were independent risk factors of CCA ($p = 0.0019$).
Conclusion: Anti-GP2 IgA/PR3 ANCA identify a subgroup of PSC patients at risk of poor outcome, more aggressive course, and biliary cancer. These antibodies may be of prognostic value in PSC.

FRI142

Analysis of 1,776 patients with primary sclerosing cholangitis from a laboratory database

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Background and Aims: The ICD-10 is an international standard for defining and reporting diseases and health conditions. Most of the epidemiologic data available in Primary Sclerosing Cholangitis (PSC), a rare cholestatic liver disease, originate from a period before the new ICD 10 code K83.01 was available. The aim of the current analysis was to evaluate laboratory and comorbidities data from patients with this PSC specific ICD 10 code.
Method: A clinical laboratory database maintained by LabCorp® was utilized to assess laboratory data of 1776 PSC patients from the United States who were seen by a health care provider between 1 Oct 2018 and 31 Aug 2019. The earliest complete assessment per patient was included in the analysis if more than one was present.
Results: The mean age of the patients was 49 years (0–92 yrs, SD 18), 44.1% were female. Alkaline phosphatase (ALP) levels were elevated in 69.7% and were >1.5 × ULN in 52.7% of the patients. Inflammatory bowel disease was reported in 25.7% (ulcerative colitis 19.0%, Crohn's disease 6.7%). Other concomitant diagnoses with a frequency >5% were fibrosis and cirrhosis of the liver (10%), abnormal serum enzyme levels (6.4%), other inflammatory liver disease (IBD, 6.1%) and abnormal results of function studies (5.7%). A comparison between female and male patients (mean age 51 vs. 47 years) revealed a higher prevalence of ulcerative colitis in males (21.6% vs. 15.7%) and a slightly higher rate of reported fibrosis and cirrhosis of the liver in males (10.8% vs. 8.9%). ALP and other laboratory parameters were comparable between the sexes. Patients with IBD had a lower rate of reported fibrosis and cirrhosis of the liver (7.2 vs. 10.9%). This was mainly attributable to a lower rate in patients with Crohn's disease compared to patients without Crohn's disease (4.2 vs. 10.4%). The highest prevalence of fibrosis and cirrhosis of the liver was seen in patients with concomitant autoimmune hepatitis (16.3 vs. 9.6%).
Conclusion: A lower rate of fibrosis and liver cirrhosis in PSC patients with concomitant Crohn's disease is consistent with previous reports. Additional analysis of the reasons for a higher proportion of women with PSC in this database than the one reported in other studies is warranted. Availability of a large clinical laboratory database may add value when assessing PSC patient characteristics.

FRI143

The treatment response and corticosteroid therapy was predicted by GGT, chol, and fibrosis in patients of PBC-AIH overlap syndrome: a real-world study

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Background and Aims: The aim of this study was to elucidate the response to corticosteroid therapy and the associated factors in

primary biliary cholangitis- autoimmune hepatitis (PBC–AIH) overlap syndrome.
Method: A cohort study was performed to evaluate the treatment response to immunosuppressive therapy and ursodesoxycholic acid (UDCA) combination in this unique group. This cohort study was performed by a retrospective analysis of prospectively documented data between October 2013 and January 2019 and included 101 patients. The primary endpoints were treatment response at 6 months. Logistic regression analysis was performed to identify factors significantly associated with treatment response.
Results: 55.4% of patients did not respond to treatment. The baseline values of serum total bilirubin, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), globulin, IgG, cholesterol (CHOL) and positivity for anti-mitochondrial antibody differed significantly between the responders and non-responders ($P < 0.05$). After multivariate analysis, high GGT levels ($P = 0.036$; odds ratio = 1.003), high CHOL levels ($P = 0.005$; odds ratio = 1.639) and presence of cirrhosis ($P = 0.005$; odds ratio = 6.424) were associated with lack of response to corticosteroid therapy. The responders have a better liver-related adverse event-free survival, compared with non-responders according to the Kaplan-Meier estimate (Log-Rank: $p < 0.001$). Second-line immunosuppressive agents (mainly mycophenolate mofetil and tacrolimus) led to biochemical remission in 65.0% of patients who did not respond to initial immunosuppression.

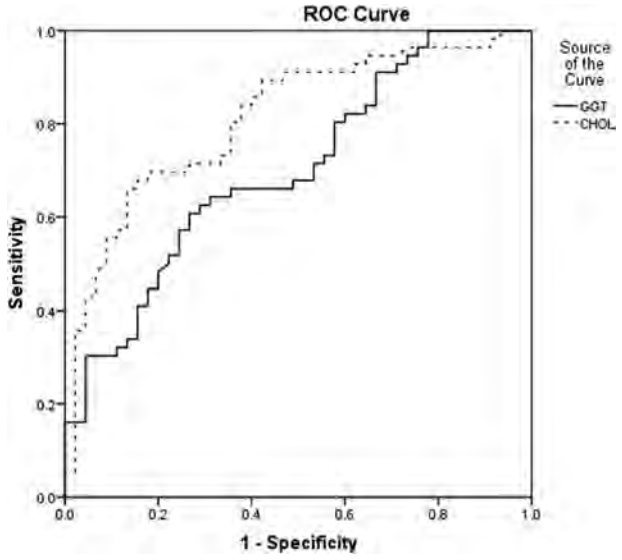

Figure 1: GGT and CHOL values showed high predictive accuracy of non-response (AUROC 0.701, 95% CI: 0.600, 0.802; AUROC 0.812, 95% CI: 0.728, 0.896; respectively), with the optimal cutoff at entry as 398 umol/L and 6.225 g/L, respectively.

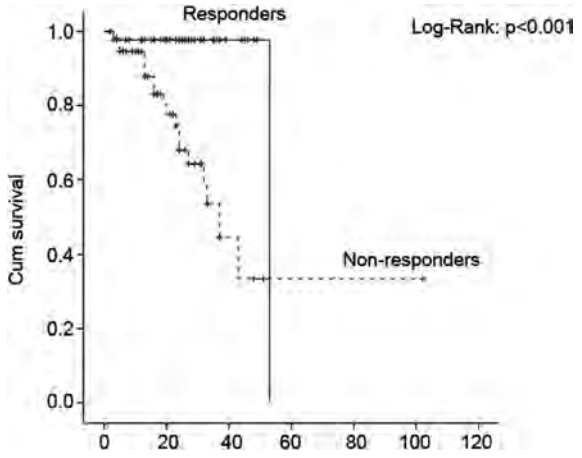

Figure 2: Kaplan–Meier analysis revealed that responders had a significantly higher liver-related adverse events-free survival rate than non-responders (Log-Rank: $p < 0.001$).

Conclusion: 55.4% of patients of PBC-AIH overlap showed poor response to corticosteroid therapy in a university hospital, and high GGT levels, high CHOL levels, and presence of cirrhosis were associated with lack of response to corticosteroid therapy. Early identification of no-response may allow timely intervention to prevent clinical deterioration. Second-line immunosuppressive agents lead to 65.0% of response.

FRI144

Risks and benefits of percutaneous transhepatic cholangiodrainage in patients with primary sclerosing cholangitis

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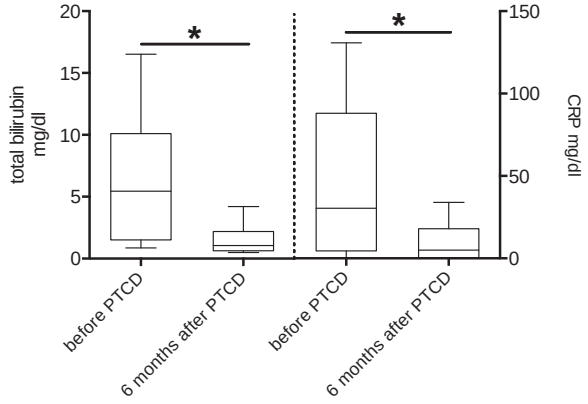
Background and Aims: Endoscopic retrograde cholangiography (ERC) is the method of choice to treat biliary strictures in patients with primary sclerosing cholangitis (PSC). However, in a subgroup of PSC patients, biliary stenoses are complex and endoscopic biliary drainage cannot be established using ERCP. There is no generally accepted recommendation how to proceed in this situation, highlighting a severe lack of data. The aim of this study was to investigate in a multicentre study the risks, benefits and clinical outcomes of PSC patients after percutaneous transhepatic cholangiodrainage (PTCD).
Method: In this retrospective study medical records were reviewed for clinical data including laboratory results, previous endoscopic interventions and intervention-related complications.
Results: A total of 37 PSC patients who underwent PTCD were identified. Strictures were localised in the common bile duct (CBD) in most of the cases (CBD = 51.4%; bifurcation = 16.2%; left = 13,5%; right = 2,7%; multiple = 16.2%). Liver cirrhosis was present in 14 patients (37.8%) with a median MELD score of 16 at the time of first PTCD. In most cases jaundice (51.2%) was the indication for PTCD, followed by recurrent bacterial cholangitis (16.3%), suspected cholangiocarcinoma (CCA, 16.3%) and pruritus (11.6%). Mild periinterventional complications occurred in 20 patients (54%; 19x bacterial cholangitis, 1x pancreatitis). Severe complications in three patients (bile duct perforation, dislocation of catheter, pleural puncture) resolved without sequelae. Overall total bilirubin and CRP levels significantly decreased six months after PTCD (Fig. 1). Pruritus improved in four of five patients after PTCD.



Conclusion: To our knowledge, this is the first multicentre study investigating clinical outcomes of PSC patients undergoing PTCD. The procedure was generally safe and mild complications prevailed. PTCD for PSC patients is effective by amending jaundice and pruritus and by improving biochemical signs of cholestasis and inflammation. These results indicate that PTCD should not be withheld from PSC patients lacking endoscopic options for biliary drainage.

FRI145

Antimitochondrial antibodies in patients with autoimmune hepatitis: a large multicenter study

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Background and Aims: Antimitochondrial antibodies (AMA) are specific for primary biliary cholangitis (PBC) diagnosis but can also be found in patients with autoimmune hepatitis (AIH). The present large multicenter study assessed the prevalence and significance of AMA in AIH-patients.

Method: 191 AMA (+) AIH-patients were investigated compared to 699 age- and sex-matched AMA (−) AIH-patients. The total number of AIH-patients followed at each center was used for evaluation of AMA prevalence. A subgroup of 774 patients with available liver biopsy was classified according to AMA and PBC histological characteristics: group A: 441 AMA (−)/Hist. (−); group B: 164 AMA (−)/Hist.(+); group C: 83 AMA (+)/Hist.(−); group D: 86 AMA (+)/Hist. (+).

Results: AMA prevalence in AIH-patients was 10.5% (range 3.7%–16.3%). Comparison of 4 groups revealed that itching was mainly associated with the presence of PBC histological characteristics (14.5% vs 32.3% vs 27.7% vs 26.7%, respectively, $p < 0.001$). Alkaline phosphatase levels (xULN) were higher in AIH-patients with PBC histological characteristics irrespective of AMA presence [1.1 (0.8) vs 1.3 (1.3) vs 1.3 (1) vs 1.4 (2), respectively, $p < 0.001$]. Anti-sp100 (3.3% vs 11.4% vs 8% vs 28%, $p < 0.001$) and anti-gp210 positivity (1.3% vs 2.9% vs 8.3% vs 21.7%, respectively, $p < 0.001$) were significantly higher in AMA (+) AIH-patients with PBC histological characteristics. AMA positivity was associated with the presence of florid duct lesions (OR 5.1, 95%CI 2.8–9.2, $p < 0.001$) and ductopenia (OR 3.3, 95%CI 1.5–8.1, $p < 0.01$). Response to immunosuppression or UDCA was similar among groups. Progression to cirrhosis during follow-up was associated only with the presence of PBC histological characteristics (HR 2.1, 95%CI 1.2–3.5, $p < 0.01$ group B; HR 1.5, 95%CI 0.7–3.2, $p = 0.3$ group C; HR 3.2, 95%CI 1.8–5.7, $p < 0.001$ group D, compared to group A respectively), while similar survival rates were found among groups. During follow-up, AMA (+) AIH-patients had higher risk to develop PBC histological characteristics (HR 3.6, 95%CI 1.4–9.3, $p < 0.01$), while resolution of PBC histological characteristics was not associated with AMA presence ($p = 0.3$).

Conclusion: AMA presence is common among AIH-patients, but their clinical significance appears to be important only when they co-exist with characteristics of PBC at the histological level. Therefore, a careful evaluation of liver biopsy for cholestatic lesions seems of outmost importance in these patients. [on behalf of International AIH Group]

FRI146

Durability of biochemical improvements through six years of open label treatment with obeticholic acid in patients with primary biliary cholangitis who did not achieve the poise criteria

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Background and Aims: In various clinical studies and in daily clinical practice, response to primary biliary cholangitis (PBC) treatment has been assessed using dichotomous biochemical response criteria. While achieving these response criteria may be associated with improved clinical outcomes, they may underestimate the benefit in patients who have an incomplete response to treatment. The objective of this analysis was to assess the extent and durability of obeticholic acid (OCA) in patients with PBC who did not achieve the dichotomous primary endpoint criteria in the phase 3 POISE study through 72 months of OCA treatment.

Method: Key inclusion criteria included PBC diagnosis, alkaline phosphatase (ALP) ≥ 1.67 × upper limit of normal (ULN) and/or total bilirubin >ULN to <2 × ULN, and on a stable dose of—or intolerant of—UDCA. During the 12 month double-blind phase, 216 patients were randomized to daily placebo, OCA 5–10, or OCA 10 mg. This analysis pooled double-blind placebo (OCA baseline was OLE day 0) and double-blind OCA patients to evaluate the efficacy and safety of up to 72 months of OCA treatment. This analysis excludes subjects who

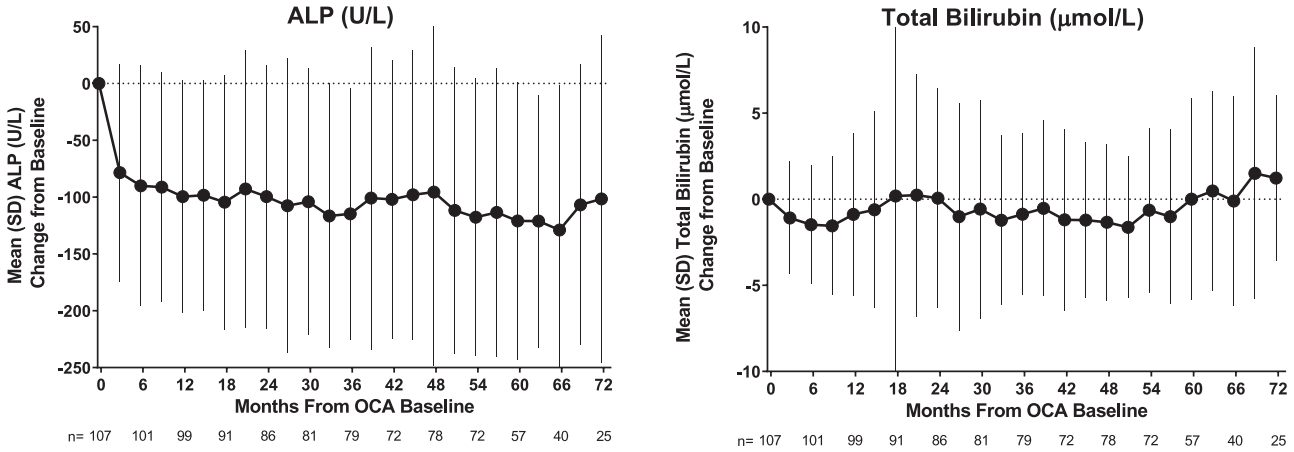

Figure 1: (abstract: FRI146): Change From Baseline in ALP and Total Bilirubin through 72 Months of OCA Treatment

achieved the POISE primary endpoint (ALP <1.67 × ULN, with a reduction of ≥ 15% from baseline, and total bilirubin ≤ ULN) 12 months from OCA Baseline. Values shown are mean (SD) unless otherwise specified. P-values were based on paired t-tests.

Results: One hundred and ninety-three patients enrolled in the OLE of which 107 patients (55%) did not achieve the POISE criteria after 12 months of OCA treatment. Patients were 93% female, 91% Caucasian, 56 (10) years of age at baseline and 91% received UDCA (15 [4] mg/kg/day). At baseline, ALP was 356 (138) U/L and total bilirubin was 13 (8) µmol/L (elevated above ULN in 18 patients [17%]). Despite not achieving the POISE criteria after 12 months of OCA, a significant and durable reduction was observed in ALP ($p < 0.01$ at all time points) through the duration of 72 months of treatment (figure 1). Total bilirubin levels remained stable and near baseline values within the normal range through the duration of treatment. Through the 6-year study period, the most commonly occurring adverse events were pruritus (92 patients [86%]) and fatigue (33 patients [31%]) consistent with previous reports from POISE and expected PBC symptoms.

Conclusion: Despite the fact that these patients did not achieve the POISE primary endpoint, significant and sustained biochemical improvements were observed.

FRI147

Enhanced liver fibrosis test and liver stiffness variation over time in a prospective cohort of primary sclerosing cholangitis patients

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Background and Aims: The clinical presentation, liver biochemistry fluctuations and progression of primary sclerosing cholangitis (PSC) is highly variable and there is a need to establish prognostic tools. The Enhanced Liver Fibrosis (ELF) test and liver stiffness measurements (LSM) have both demonstrated strong predictive abilities/association with transplant-free survival in PSC, which was validated in independent studies; however, whether ELF and LSM fluctuate and how they vary over time is not well described. We aimed to characterize ELF and LSM variation over time in a prospective PSC cohort.

Method: We included 120 non-transplant PSC patients (90 males [75%]; mean age 43.7+/−15.4 years; n = 87 [72.5%] had inflammatory bowel disease [IBD]) followed prospectively at annual study visits between 2013 and 2019 in the Norwegian PSC Research Center prospective cohort. ELF test, clinical data, liver biochemistries and liver stiffness measurement (LSM) by point shear wave elastography were included from all available visits. Revised Mayo risk score was calculated using the published algorithm. We performed statistical analysis using a generalized mixed model in STATA version 16.0.

Results: At baseline, PSC patients were characterized by mean ELF of 9.46+/−1.17 and median LSM of 1.25 m/s (range 0.66–3.04 m/s). ELF score was significantly higher (10.67 vs 9.11; $p < 0.001$) in patients with advanced (F3-F4; LSM >1.79 m/s; n = 24) compared to mild-moderate fibrosis (n = 92) as defined by LSM applying published cutoff values for transient elastography. ELF increased significantly over time (0.06 per year, CI [0.01, 0.10], $p = 0.013$), with an intraclass correlation (ICC) of 0.76, indicating that 76% and 24% of ELF variation was explained by between- and within-patient effects, respectively. LSM increased over time ($p = 0.04$) with a larger influence of within-patient effects (ICC 0.53). ELF, but not ALP, was associated with LSM variation. In multivariate analysis of longitudinal data, ELF test was more strongly associated with Mayo risk score than ALP and LSM.

Conclusion: ELF test and LSM increased during 5-year follow-up in PSC, with a stronger effect of between-patient variation for ELF than for LSM. Both between- and within-patient effects of ELF were associated with Mayo risk score and ELF test was more strongly associated with Mayo risk score compared to LSM and ALP. Our results may indicate that ELF is a more robust predictor in PSC compared to LSM.

FRI148

An international perspective on cholestatic pruritus in primary biliary cholangitis (PBC)

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Background and Aims: This survey of physicians treating patients with PBC and cholestatic pruritus aimed to provide information about the presentation and severity of pruritus and its management in clinical practice and the broader symptom burden of PBC internationally.

Method: This was a multinational survey of 68 Gastroenterologists and Hepatologists across US, Germany, China and Japan (funded by GSK). Participating physicians were asked to complete 3 patient record forms (PRFs) for patients with PBC and cholestatic pruritus, including ≥ 1 receiving a second line PBC treatment.
Results: Completed PRFs were provided for 164 patients; 83 in the US, 33 in Germany, 29 in China and 19 in Japan. The majority of patients (81%) were over 40 yrs. Patients in Japan were notably older than in other countries.
Overall 69% of patients were reported to have intermittent pruritus and 31% chronic pruritus. The proportion with chronic pruritus was highest in China (38%) and lowest in Japan (16%). Patients with chronic pruritus tended to be younger. The majority of patients had mild (48%) or moderate (46%) pruritus with only 6% reported to have severe pruritus. Patients with severe pruritus were younger than those with mild or moderate pruritus; in this sample no patients over 60 yrs had severe pruritus and older patients (71+ yrs) all had mild pruritus.
Fatigue was consistently the most reported other symptom in this sample of patients (70%). The reported symptom profile was similar in US and Germany. Fewer symptoms were reported for Japanese patients and the China symptom profile was notably different with a higher report of jaundice (76%) compared to other countries (11–21%). Presence of other symptoms tended to be higher in patients with more severe pruritus, in particular; dry eyes, emotional stress, jaundice, sleeping difficulties and dry mouth.

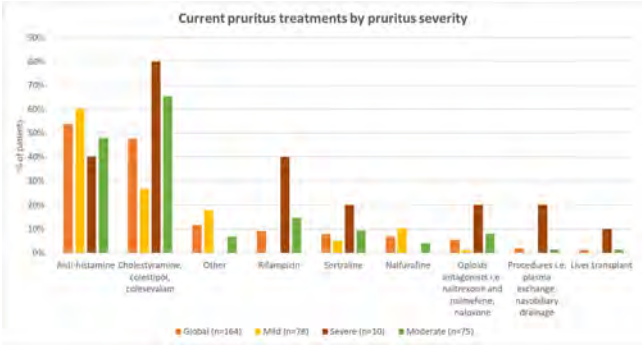

Figure: Current pruritus treatment by pruritus severity.

Overall cholestyramine and anti-histamines were the most common pruritus treatments; except in Japan where patients were prescribed nalfurafine or anti-histamine. Patients with mild pruritus were more commonly treated with anti-histamine and to a lesser extent cholestyramine (Figure), whereas more severe patients were more likely to receive all the treatments (except anti-histamine) and receive multiple treatments. The mean number of treatments (class) concurrently prescribed per patient by pruritus severity was 1.22 mild, 1.59 moderate, and 2.30 severe, and by country 1.59 US, 1.12 Germany, 1.72 China and 1 Japan.
Conclusion: This international survey of physicians identified notable differences in both the presentation and the management of cholestatic pruritus in patients with PBC internationally. These data underscore the burden of cholestatic pruritus in PBC, particularly for those patients with severe pruritus. Regardless of pruritus severity most patients with pruritus also suffer with fatigue.

FRI149
Magnetic resonance imaging features of primary biliary cholangitis
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Background and Aims: Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease characterized by slow progression of cholestasis and the development of liver fibrosis. Imaging features described in the literature were nonspecific till the first specific imaging finding "periportal halo sign" was described. In this study, we aimed to evaluate MRI features of the liver in PBC patients in a large cohort and also correlate the features in a subgroup of patients with histological findings on liver biopsy performed within 6 months of MRI studies.
Method: We conducted a multicenter retrospective review on 283 patients with PBC who underwent an MRI. MRI studies were reviewed by two abdominal radiologists in consensus for liver morphology, signal intensity, post-contrast enhancement and signs of decompensation. Liver and spleen volumes and normalized liver apparent diffusion coefficient (nlADC) were also calculated. MRI features were correlated with fibrosis stage among a subset of patients who had a liver biopsy within 6 months (n = 72).
Results: The study population comprised of 253 (89%) females and a mean ± SD age of 59.4 ± 11.8 years. Lymphadenopathy (78.1%), periportal hyperintensity (36.7%), and periportal halo sign (27.6%) were most common features. A positive correlation was found between fibrosis stage and spleen size ($r = 0.457$, $p < 0.001$), spleen volume ($r = 0.557$, $p < 0.001$) and portal vein diameter ($r = 0.287$, $p = 0.013$) and a negative correlation with nlADC ($r = -0.332$, $p = 0.011$). Fibrosis stage also correlated with presence of surface nodularity ($p < 0.001$), periportal halo sign ($p = 0.04$), collaterals ($p = 0.033$) and splenomegaly ($p = 0.002$). No significant differences in nlADC values were found in different fibrosis stages. The periportal halo sign was present in only patients with significant fibrosis. None of the MRI features significantly correlated with inflammation grade.
Conclusion: In PBC, presence of periportal halo sign correlates with significant fibrosis. Heterogeneous T2W intensity, heterogeneous post-contrast enhancement, spleen size, spleen volume correlate with fibrosis stages and may be useful for predicting advanced fibrosis.

FRI150
Comparison of liver stiffness measurement with MRE and liver and spleen volumetry for prediction of disease severity and hepatic decompensation in patients with primary sclerosing cholangitis
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Background and Aims: Primary sclerosing cholangitis (PSC) is a chronic liver disease characterized with bile duct inflammation and fibrosis leading to cholestasis and parenchymal injury. The aim of this study was to evaluate liver stiffness measures (LSM) with magnetic resonance elastography (MRE) and volumetry measurements of liver and spleen and their correlation with disease severity and prediction of hepatic decompensation.
Method: This retrospective study was approved by the institutional review board. Magnetic resonance imaging (MRI) and MRE studies were reviewed and mean liver stiffness of entire liver, right lobe and left lobe, total liver, right lobe, left lobe, caudate lobe and spleen volumes were calculated. Qualitative evaluation of lobar atrophy or hypertrophy and presence of macronodular regeneration (MNR) was recorded. Univariate and multivariate analyses were performed to predict hepatic decompensation.

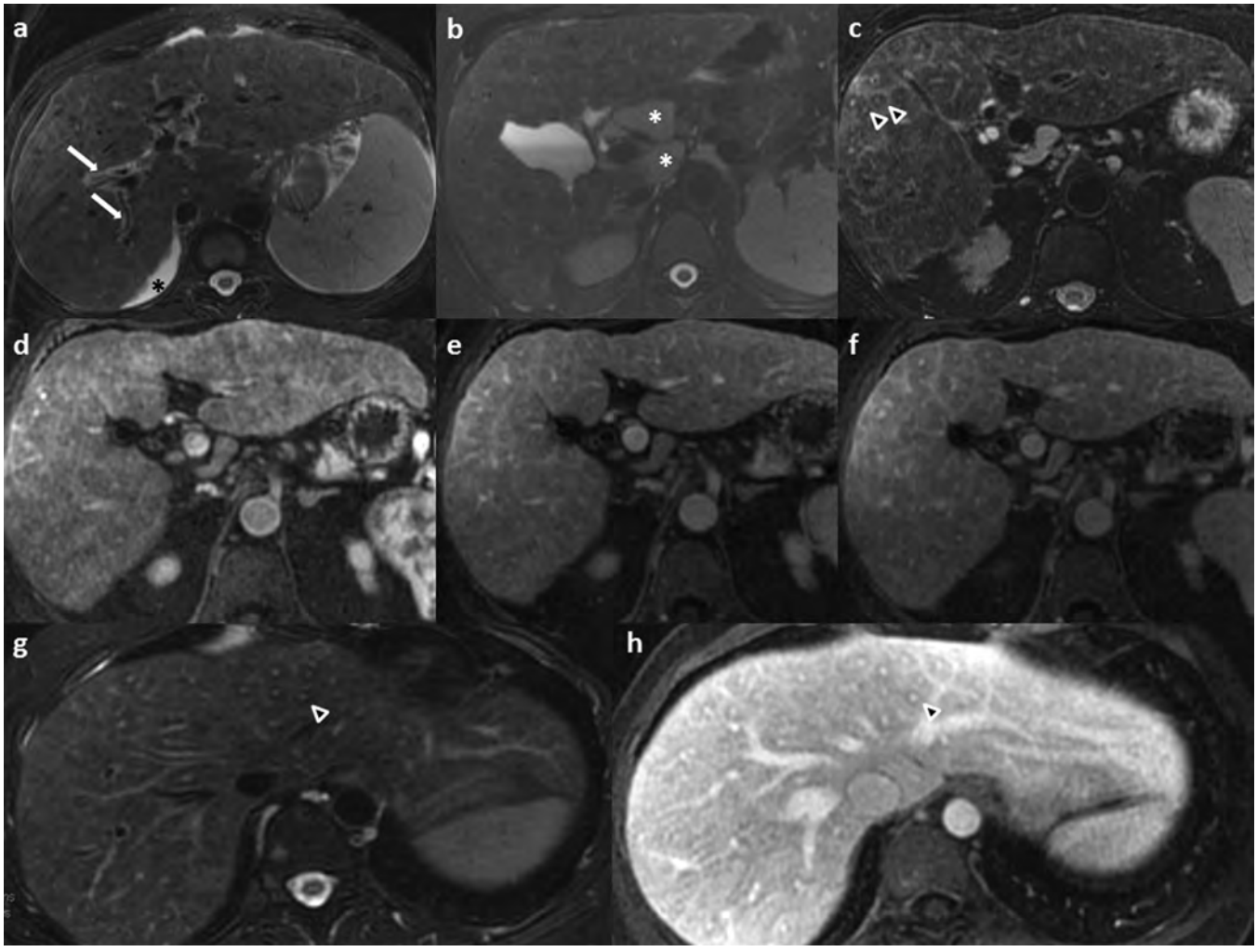

Figure 1: (abstract: FRI149): Typical MRI findings in PBC illustrated with examples from different patients. (a) A T2W image in a patient with stage 4 fibrosis shows periportal hyperintensity and T2 signal heterogeneity of the liver parenchyma. Ascites (*) and surface nodularity is also seen. (b) Enlarged lymph node (*) in the portal hilum is seen on T2W image of a different patient with stage 3 fibrosis. Images from another patient with stage 4 fibrosis demonstrating heterogeneity and periportal halo sign (arrow-heads) on T2W image (c), heterogeneity on post-contrast arterial phase (d), portal venous phase (e) and delayed phase images (f). A patient with periportal halo sign on T2W image (g) and post-contrast venous phase image (h) (arrow heads).

Results: A total of 266 patients with PSC were included in the study. Lobar stiffness measures were higher in the presence of relative lobe atrophy. Mean LSM was higher in the presence of MNR. Significant correlations were observed between mean LSM and volumetry measurements with a fair correlation between LSM and spleen volume ($rs = 0.526$, $p < 0.0001$). Among the measurements, the best correlation was observed between mean LSM and Mayo risk score ($rs = 0.646$, $p < 0.0001$). In the multivariate analyses, mean LSM and Mayo risk score were significantly associated with the liver decompensation (hazard ratio, 1.18; 95% CI, 1.02–1.36 and hazard ratio, 1.65; 95% CI, 1.08–2.53, respectively).
Conclusion: LSM with MRE performs significantly better than liver and spleen volumes for prediction of both disease severity and hepatic decompensation.

FRI151

The inter-relationship between primary sclerosing cholangitis and socioeconomic status

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Background and Aims: Disease clustering in primary sclerosing cholangitis (PSC) is seen in less socioeconomically deprived areas. This study aimed to explore which components of socioeconomic status either drive disease or may protect against it.
Method: All patients with PSC ($n = 472$) in a defined geographical region within England were identified using multi-source case-finding methodology. Besag-York-Mollie models were used to estimate relative risk in postcode districts and fitted with measures of social deprivation. A greater Townsend Score implies greater deprivation. A lower Index of Multiple Deprivation (IMD),

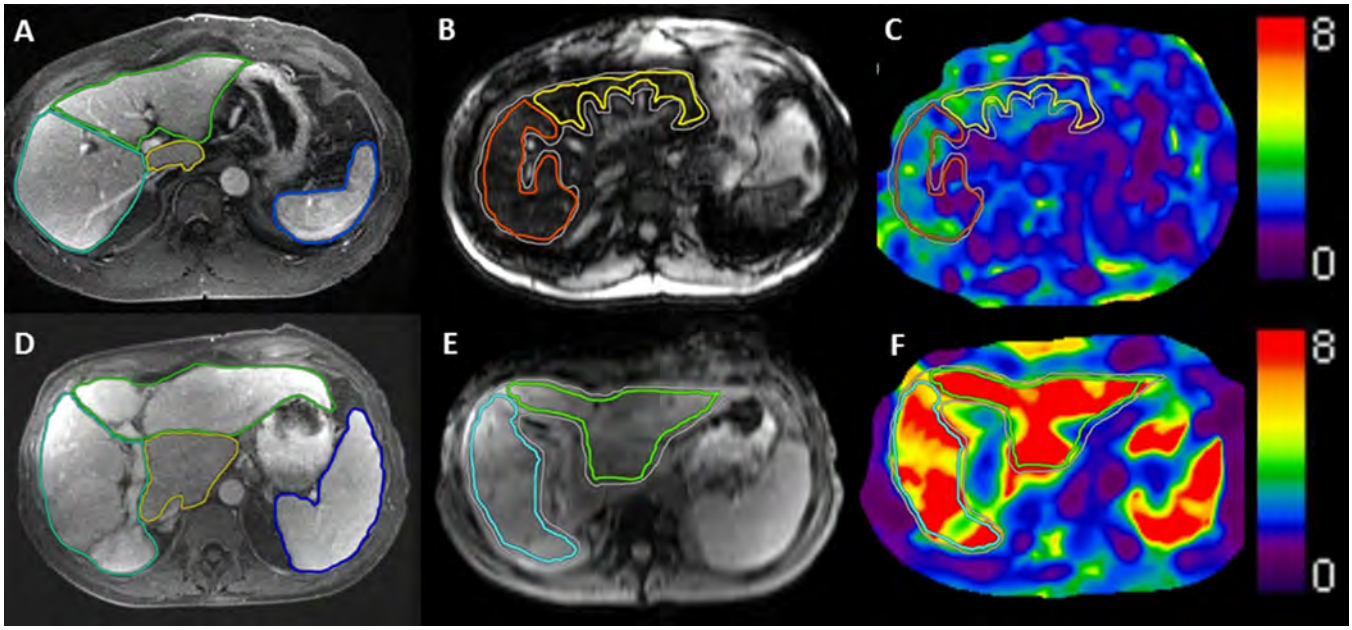

Figure 1: (abstract: FRI150): Axial post contrast T1 weighted image in the portal venous phase and MRE sequences showing the morphological and elastogram differences between 2 patients. The top row shows a 45 year old female patient with mild PSC (Mayo risk score –0.25) with right lobe volume (turquoise outline) was 986 ml, left lobe volume (green outline) was 409 ml and the caudate lobe volume (yellow outline) was 33 ml. The spleen volume (dark blue outline) measured 205 ml (Figure 1A). Figure 1B shows the magnitude image of the elastogram with ROIs for the total liver stiffness (white line), right lobe stiffness (orange line) and the left lobe (green line). The corresponding ROIs on the elastogram (Figure 1C) yielded the stiffness values as follows LSM = 1.99 kPa, RLSM = 2.12 kPa, LLSM 1.79 kPa. The bottom row shows a 65 year old patient with severe PSC (Mayo risk score 2.75). The right lobe volume was 290 ml, left lobe volume was 1364 ml and the caudate lobe was 362 ml. The spleen volume was 870 ml. The liver showed increased liver stiffness with the LSM measuring 9.47 kPa, RLSM measuring 11.82 kPa and the LLSM measuring 8.99 kPa.

constructed from 7 domains, equates to more deprivation. A change in Deviance Information Criterion (DIC) >2 indicates significant improvement in model performance.

Results: A higher risk of PSC was seen in significantly less deprived areas:

- Townsend score –3.27 to –0.46 (–2.205) in 'highest' risk areas vs –3.12 to 10.87 (4.615) in 'lowest' (p = 0.0002)
- IMD 13340 to 27960 (18685) in 'highest' risk vs 68 to 29070 (8220) in 'lowest' (p = 0.0099)

Disease risk was associated with more affluent areas with a healthier population, less crime and more expensive housing (Table 1). 'Health' refers to years of potential life lost, emergency hospital admissions and prevalence of mood disorders.

Table 1: DIC scores for null model, Townsend score and IMD domains

	2.50%	median	97.50%	DIC	Significant model improvement	Change in DIC
Null				577.2		
Townsend Score	–0.119	–0.063	–0.012	574.4	YES	2.78
Income	–2.816	–1.458	–0.057	575.2	YES	1.95
Employment	–3.676	–1.659	0.207	577.1	NO	0.07
Health	–0.455	–0.240	–0.048	573.5	YES	3.60
Education	–0.015	–0.006	0.001	576.2	NO	0.96
Crime	–0.382	–0.202	–0.020	574.4	YES	2.78
Housing	0.008	0.022	0.033	573.8	YES	3.33
Environment	–0.014	0.002	0.019	577.5	NO	–0.34

Conclusion: This work identifies particular components of socio-economic status that may be relevant to disease risk. They may be surrogate markers for disease mechanisms that reflect environmental factors linked to PSC. The association with crime may be a third party phenomenon (or not at all related) i.e. a surrogate marker for less affluent areas. It could also be that factors associated with more deprivation are protective. For example, smoking is reported in some studies to be less prevalent in PSC patients or only those with associated inflammatory bowel disease. It would also be valuable to investigate for associations between deprivation, timing of diagnosis and class mobility.

FRI152

Change in risk of primary biliary cholangitis is associated with the evolution of coal mining

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Background and Aims: Disease clustering in primary biliary cholangitis (PBC) is associated with coal-mining activity. In the UK, there were marked changes in the type of coal mined throughout the 20th century with development of the National Coal Board (NCB) with associated safety legislation in 1950 and a revolution in the technology used in the 1960s. This study aimed to explore which aspect of coal mining is specifically related to PBC risk.

Method: All patients with PBC (n = 2150) in a defined geographical region within England were identified using multi-source case-finding methodology. Besag-York-Mollie models were used for area-based modeling to estimate relative risk in postcode districts and fitted with the number of coal-mines open in 1920, 1950, 1960 and 1970 (data from the BRITPITS database). A change in Deviance Information Criterion (DIC) >2 indicated significant improvement in model performance. Structural equation modelling (SEM) was used to explore relationships between eras of coal-mining and disease risk.

Root Mean Square Error of Association (RMSEA) <0.05 with covariates significant at the 95% level and comparative fit index (CFI) were used to assess model fit.

Results: All eras of coal-mines were associated with an increased risk of PBC. Using area-based analyses, the best model was using 1950 coal-mines. When using SEM to assess multivariate relationships, coal-mines contributed up to 45% of the variation in disease risk for PBC (Table 1).

Table 1: Summary of results of area-based modelling and SEM

			Area-based modelling		SEM
	Number of open mines	Key change in coal mining	DIC score	Change in DIC	Contribution from mines
Null model			799.755		
1920 mines	1311	Peak coal production	793.508	6.247	38%
1950 mines	727	NCB opened	791.525	8.23	41%
1960 mines	501	Change in mines technology	792.797	6.958	45%
1970 mines	163	End of coal mining	802.838	−3.083	37%

Conclusion: Anthropogenic disturbance of the landscape may take years to have a detectable, clinical effect with the impact of more polluting coal-mining techniques in the early 20th century being seen decades later. It may be that long-term, low-level exposure to xenobiotics associated with coal-mining activity is implicated in disease risk. The decline in disease risk seen with 1970 coal-mines may reflect decreasing exposure to pollutants as coal-mining activity dropped and safety legislation had led to improved coal-mine administration and cleaner processing methods. There is a need to explore whether it is coal itself, mining processes or local environmental contamination that are relevant in disease development.

FRI153

The simple cholestatic complaints score is a valid and reliable questionnaire for cholestatic symptoms in PSC patients

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Background and Aims: Patients with primary sclerosing cholangitis (PSC) often suffer from cholestatic symptoms such as pruritus, fatigue and abdominal pain. There is an important unmet need for reliably measuring symptoms and disease burden in clinical trials and daily practice. The Simple Cholestatic Complaints Score (SCCS) is a 4-item questionnaire measuring pruritus, right upper quadrant pain, fatigue, and fever in PSC patients. The aim of this study is to evaluate the reliability and validity of the SCCS.

Method: The study population consists of 212 patients from the Dutch prospective PSC registry. Data were collected via digital surveys. The FDA guideline for Patient Reported Outcome (PRO) development was followed. Reliability was evaluated by internal consistency (Cronbach's-alpha) and test-re-test reproducibility (intraclass correlation coefficient (ICC)). Cronbach's-alpha >0.7 and ICC >0.7 are considered as good internal consistency and reproducibility, respectively. Face and content validity was assessed by an expert panel and based on literature. The SCCS items were compared to corresponding gold-standard measurements to determine criterion validity. A correlation >0.7 is considered as good criterion validity. Construct validity was assessed by evaluating a priori hypothesized correlations with other relevant questionnaires. If more than 75% of all correlations were as hypothesized construct validity is considered good. Discriminant and convergent validity were assessed by comparing SCCS scores in clinically different (i.e. SD-PSC vs LD-PSC) and clinically comparable (PSC-IBD vs PSC) groups. The ability to detect change was evaluated in a cohort with patients that underwent endoscopic intervention.

Results: A total of 153 patients (72%) completed the questionnaire. Demographics were representative of the general PSC population. Internal consistency was moderate and increased to 0.708 after removal of the fever item. The test-re-test reproducibility was high (ICC = 0.96). Criterion validity was good (all >0.82). Construct validity was in line with a priori hypothesized correlations in 80%. SCCS scores were different in clinically different groups and the same in patients with and without IBD. Scores of individual questions and the sum score decreased after endoscopic intervention in successfully treated patients.

Conclusion: The SCCS is a valid and reliable instrument to measure cholestatic symptoms in PSC patients. Because of its quick and easy to use properties it is highly suitable for frequent monitoring of symptoms in clinical trials and daily practice.

FRI154

The clinical significance of programmed cell death-1 rs11568821 and interleukin-28b rs12979860 polymorphisms in autommune hepatitis

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Background and Aims: Autoimmune hepatitis (AIH) is a chronic liver disease of unknown aetiology characterized by dysregulation of T-cell immunity. Programmed cell death-1 (PD1) protein is involved in immunotolerance by down-regulating effector T-cells. The single nucleotide polymorphism (SNP) PD1.3 (rs11568821, G > A) is associated with susceptibility to systemic lupus erythematosus. Furthermore, the coincidence of non-alcoholic liver disease (NAFLD) in AIH is 20–30%. The polymorphism interleukin-28B (IL-28B) rs12979860 (T > C) is associated with steatosis in HCV infection and lobular inflammation and fibrosis in NAFLD. Our aim was to investigate the prevalence and clinical significance of PD1.3 rs11568821 and IL28B rs12979860 SNPs in AIH.

Method: 125 patients followed in our Centre with AIH according to the EASL Clinical Practice Guidelines were evaluated. 100 healthy subjects were used as controls (HC). Polymorphisms were assessed with in-house allelic discrimination end-point PCR.

Results: 2/125 (2%) AIH patients were PD1.3 homozygotes AA and 22/124 (18%) heterozygotes GA vs 2/100 (2%) AA and 27/100 (27%) GA in the HC group (p = 0.2). The AA/GA genotypes were not associated with the mode of presentation of AIH, the histological grade/stage, the presence of cirrhosis, decompensation risk, response to treatment and prognosis (p > 0.1 each). Furthermore, 47/125 (38%) AIH patients were IL28B CC, 62/125 (49%) CT and 16/125 (13%) TT vs 42/100 (42%) CC, 42/100 (42%) CT and 16/100 (16%) TT in the HC group (p = 0.5). 32/125 (26%) AIH patients had concomitant NAFLD (25 steatosis and 7 steatohepatitis). NAFLD coexistence was not related to any genotype (p = 0.7). In a subgroup of 118 patients with available baseline liver biopsy, CC/CT genotype was more likely to present with advanced fibrosis (F3/F4) at baseline: 37/102 (36%) in CC/CT vs 1/16 (6%) in TT, p = 0.03. In addition, TT homozygotes were more likely to achieve complete response on treatment [10/16 (62.5%) in TT vs 38/105, (36%) in CC/CT, p = 0.04], although no difference was found between the two groups in regard to achievement of complete treatment withdrawal (p = 1.0). Survival free of liver transplantation was not affected by either genotype (p = 0.3).

Conclusion: Although the PD1.3 variant was not related to AIH susceptibility and prognosis, the IL28B rs12979860 CC/CT genotypes were associated with advanced fibrosis and lower rates of response during treatment, suggesting a potential new biomarker for AIH.

FRI155

Histological characteristics of primary biliary cholangitis with an incomplete response to ursodeoxycholic acid

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Background and Aims: Ursodeoxycholic acid (UDCA) is used as the first-line therapy for primary biliary cholangitis (PBC); it is effective for most patients. Although approximately 20% patients are incomplete response to this treatment, the clinicopathological features of these patients are unknown. A clinical trial in patients with PBC with an incomplete response to UDCA examined their liver histology to clarify predict findings for UDCA-unresponsiveness.

Method: Liver biopsy specimens from 33 patients with PBC elevated alkaline phosphatase of at least 1.67 times the upper normal limit despite UDCA were collected and classified as per the classical classification (Scheuer classification, stages 1–4). Disease activity and staging were characterized using our grading and staging system (Nakanuma classification). Chronic cholangitis with periductal lymphoplasmacytic infiltration, including chronic non-suppurative destructive cholangitis and combined activity of interface hepatitis and lobular hepatitis, were categorized into 4 grades as per the degree and distribution (CA0-3 and HA0-3, respectively). For staging, 3 criteria (fibrosis, bile duct loss, and orcein-positive granules) were independently scored (0–3) as per their degrees; a final stage score was created from the sum.

Results: Bile duct loss and hepatitis activity on HE stain and orcein-positive granules on orcein stain were relatively prominent compared with those of the general PBC population in our routine practice. CA0/1/2/3 cases were distributed as 55%, 15%, 3%, and 27%, respectively. CA0 cases were prominent because of marked bile ducts loss. HA0/1/2/3 cases were 0%, 27%, 48%, and 24%, respectively, with a prominence of cases categorized with moderate hepatic activity. The distribution of stages 1–4 as per Nakanuma classification considerably differed from that as per Scheuer classification. Although with Scheuer classification, stage 1/2/3/4 cases were distributed as 36%, 24%, 30%, and 9%, respectively, with Nakanuma classification, they were distributed as 0%, 3%, 15%, and 82%, respectively, indicating that most were advanced cases. Among 3 criteria defining stage, particularly, the scores of bile duct loss and orcein-positive granules were higher than that of fibrosis.

Conclusions: The histology of PBC with an incomplete response to UDCA was characterized by marked hepatitic activity, bile duct loss, and orcein-positive granules. The Scheuer classification could not reflect these features, but the Nakanuma classification accurately showed the pathological condition of PBC, including prognostic prediction of UDCA treatment.

Nakanuma classification							
CA0	55%	HA0	0%				
1	15%	1	27%				
2	3%	2	48%				
3	27%	3	24%				
Stages		Bile duct loss		Orcein-positive granules		Fibrosis	
Stage 1	0%	Score 0	3%	Score 0	0%	Score 0	0%
2	3%	1	3%	1	3%	1	39%
3	15%	2	18%	2	24%	2	42%
4	82%	3	76%	3	73%	3	18%
Scheuer classification							
Stage 1	36%						
2	24%						
3	30%						
4	9%						

FRI156

Maternal and foetal outcomes, biochemistry and immunology changes during pregnancy in patients with autoimmune hepatitis

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Background and Aims: Autoimmune hepatitis (AIH) is an immune mediated liver disease predominantly affecting women. It is challenging to manage, especially during pregnancy. Our aim was to observe the clinical outcomes, biochemistry and immunology changes occurring during pregnancy and in the six months following delivery in patients with AIH.

Method: We reviewed the records and collected data for 16 women (26 pregnancies) with well-defined AIH who had experienced a pregnancy (including miscarriages and stillbirths) while under the care of our unit over a 10 year period. Rates of change in blood markers over the antenatal period were assessed using general linear models or log-linear models where appropriate. The models were then extended to assess post-natal trends using an interrupted time series approach, comparing ante- and postnatal blood markers, rates of change and any step-changes occurring immediately after delivery.

Results: Data were available for N = 26 pregnancies in N = 16 patients (with data for 5 further pregnancies in the process of being collected). The majority of pregnancies were Type 1 AIH (N = 21). Ten pregnancies occurred in the presence of liver cirrhosis. The majority of pregnancies resulted in a live birth (N = 20), while two resulted in miscarriage and one in a still-birth (three pregnancies ongoing). Of live births, 30% were premature and 65% were delivered via caesarean section. A total of N = 64 blood samples were taken during the antenatal period. ALT, AST, Bilirubin, IgG and INR decline significantly during pregnancy (all $p < 0.001$). Using data from live births (N = 20), trends in blood markers over the ante and post-natal periods were assessed. ALT and IgG declined significantly across the antenatal period by an average of 9.1% and 4.6% per month respectively ($p = 0.033$ and $p < 0.001$). Following delivery, ALT levels showed a step-change increase of 124% ($p = 0.007$), while IgG showed a 34.2% ($p < 0.001$) step-change increase (see Figure). Post-partum flare occurred in 52% of pregnancies.

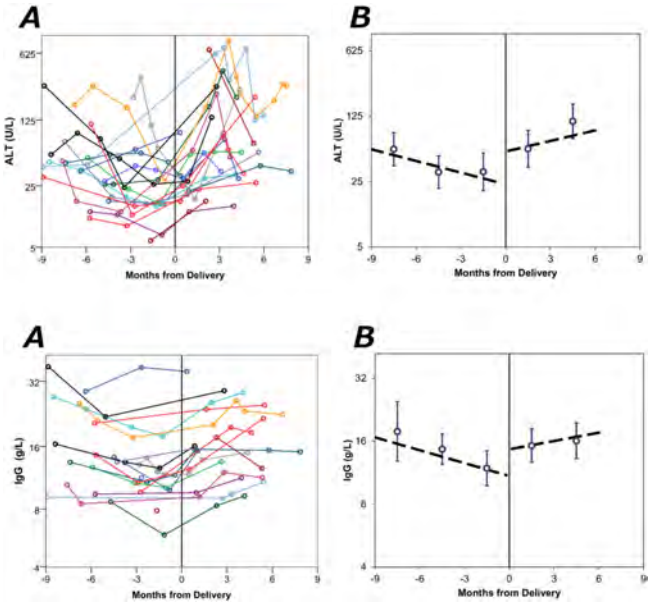

Figure: Trends in blood markers during ante- and post-natal periods: y-axis uses a logarithmic scale. Negative values are antenatal and positive are postnatal. Figure A shows the trajectories for each pregnancy (live births). In Figure B, points represent the geometric mean ALT/ IgG within three-monthly intervals, which are plotted at the midpoint of the interval (whiskers represent 95% confidence intervals). Broken lines represent interrupted time series models.

Conclusion: Biochemical and immunological remission occurs during pregnancy. Post-partum flare is common, being observed in half of the pregnancies. Pre-pregnancy counselling and management of this unique patient cohort with obstetric-liver multi-disciplinary team is crucial. Additionally, dissecting the immune mechanism is crucial to understanding and preventing post-partum flare ups.

FRI157

Impaired sulfation capacity may deteriorate clinical course in patients with primary sclerosing cholangitis (PSC)

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Background and Aims: Chronic cholestasis induces pregnane-X-receptor (PXR) which orchestrates various detoxifying processes. These include activation of sulfotransferase 2A1 (SULT2A1), an enzyme which facilitates sulfation, a critically important mechanism of elimination of endo and exotoxins. It has been previously shown that SULT2A1 activation is specifically impaired in PSC but not in another cholestatic condition, namely PBC. In this study we analyzed serum levels of dehydroepiandrostendione sulfate (DHEA-S), a marker of sulfation capacity in a large cohort of patients with PSC and correlated it with various clinical features.
Method: We included 307 patients with PSC (215 males, median age 32 years). Seventy one subjects had additional features of autoimmune hepatitis (AIH/PSC). Health-related quality of life (HRQoL) in PSC patients was evaluated with SF-36/PBC-40. Control group comprised of 104 patients with HCV (83 males, median age 41 years). Mann-Whitney, Spearman correlation and Fisher exact tests were applied as appropriate. Stepwise logistic regression analysis was used to indicate independent variables determining decreased DHEA-S
Results: Eighty three (27%) PSC patients had decreased DHEA-S, as compared to 10 (9.6%) in controls ($p = 0.0002$). Patients with PSC and decreased DHEA-S levels had significantly worse laboratory parameters including lower albumin/bilirubin ($p < 0.001$ for both); higher MELD scores ($p < 0.01$), and INR ($p < 0.001$). They also had significantly impaired PBC-40 Social Emotional (PBC-40) and Physical Functioning (SF-36) domains. Decreased DHEA-S level was associated with younger age at diagnosis ($p < 0.001$); female gender ($p < 0.05$), the presence of cirrhosis ($p < 0.01$) and PSC/AIH ($p < 0.0001$). No association between decreased DHEA-S and the presence of concomitant inflammatory bowel disease ($p = 0.65$) was seen. In multivariate analysis, higher MELD (OR = 1.219, 95% CI 1.09–1.363, $p < 0.001$), female gender (OR = 3.122, 95% CI 1.60–6.11, $p < 0.005$), younger age (OR = 3.12, 95% CI 1.60–6.11, $p < 0.01$) and AIH/PSC ($p < 0.0001$) but not liver cirrhosis were found as independent risk factors for decreased DHEA-S level.
Conclusion: Significant proportion of patients with PSC presents with low levels of DHEA-S reflecting impaired sulfation processes. These patients have significantly worse course of their disease. Impaired sulfation could be considered as one of contributing factors in a clinical progression of PSC.

FRI158

Accuracy of liver stiffness measurement in assessing liver fibrosis in naive patients with primary biliary cholangitis

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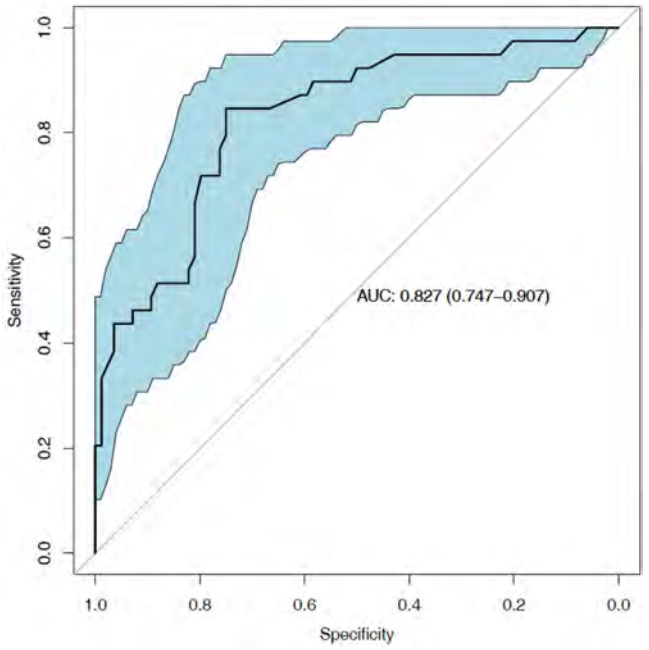
Background and Aims: Non-invasive evaluation of liver fibrosis in primary biliary cholangitis (PBC) with Liver Stiffness Measurements (LSM) by Transient Elastography (TE) is routinely undertaken at diagnosis for disease staging and risk stratification. However, evidence on correlation between LSM and liver fibrosis is based on cross-sectional studies in PBC-treated patients. Moreover, the impact of potential confounders, e.g. cholestasis and steatosis, is unclear.
Aim of our study was to investigate the accuracy of LSM to predict moderate to severe fibrosis in newly diagnosed PBC patients naïve to therapy.

Method: We collected data from 182 adult patients who underwent liver biopsy (LB) for PBC at diagnosis in five Italian liver centers from Jan 2006 through Aug 2019. TE examinations within 3 months from LB were included. LB were scored centrally by two expert pathologists, blinded to clinical data and disease stage, according to Ludwig staging system. In all patients Fibrosis-4 (FIB-4) and aspartate aminotransferase [AST]/platelet ratio (APRI) score have been calculated. Diagnostic accuracy of LSM, FIB-4 and APRI score was estimated using the area under the receiver operating characteristic curves (AUROCs) for fibrosis. The effects of liver biochemistry and histological parameters were appraised using multivariable logistic model.
Results: 123 PBC patients had adequate LB (≥9 portal tracts) and valid LSM values. According to histological assessment, Ludwig stage distribution was as follows: stage I = 38 (30.9%), stage II = 46(37.4%), stage III = 27 (21.9%), stage IV = 12 (9.8%). TE identified patients with Ludwig stage III/IV with an AUROC of 0.83 (95% confidence interval [CI] (0.74, 0.90)) (Figure). The optimal threshold was identified at 6.75 kPa (CI (6.55, 7.50)), with 85% of sensitivity, 75% of specificity, 78% of accuracy and 6 false negative. TE was superior to APRI and FIB-4 having AUROC of 0.638 (CI = (0.535, 0.740)) and 0.641 (CI = (0.516, 0.766)), respectively. At multivariable analysis only LSM was associated with liver fibrosis and no significant effect of biochemical measures and steatosis was found.



Conclusion: LSM is accurate to predict moderate to severe liver fibrosis at diagnosis in PBC naïve patients using a threshold of 6.75 kPa with an AUROC of 0.83. TE outperformed FIB-4 and APRI score and is not confounded by liver biochemistry and steatosis. These data can inform strategies for patient surveillance and trial design in PBC.

FRI159

Ciprofibrate: a new option of fibrate for primary biliary cholangitis with incomplete response to ursodeoxycholic acid

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Background and Aims: Bezafibrate and fenofibrate both have substantial evidence of anticholestatic properties in patients with primary biliary cholangitis (PBC). Ciprofibrate, one of the most potent peroxisome proliferators, had never been studied in this scenario. Our goal was to describe an experience with ciprofibrate in PBC with incomplete response to UDCA.
Method: A retrospective study was conducted with 40 patients (38 women) with cholestasis and anti-mitochondrial antibody reactivity with incomplete UDCA response (Paris II criteria). Ciprofibrate was combined at a daily dose of 100 mg between 2013 and 2017, and patients were followed until May 2019. Blood samples were obtained at diagnosis, after 12 months of UDCA use and at 3, 6, and 12 months after combination with ciprofibrate. We compared laboratory tests by paired two-tailed T-test, and $p < 0.05$ was considered significant.
Results: Mean age at diagnosis was 44.8 years; 3 patients (9.4%) had cirrhosis and 23 (57.5%) had moderate to severe pruritus. UDCA reduced the levels of alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TB) and reduced partially pruritus in 23 patients (74.2%), and completely in 8 (25.8%). Association with ciprofibrate reduced ALP and GGT at 12 months, 83.9% had complete response and after one year 37.5% of patients had ALP, GGT, AST, ALT, TB, albumin and prothrombin index normalized. It also fully eliminated itching in 81% of patients who still had itching under UDCA. The ciprofibrate dose was reduced to 100 mg every other day in 14 patients (35%) after an average of 12 months and was withdrawn in 14 (35%) after an average of 13 months. The main side effects were myalgia, hepatitis, dyspepsia, increased creatinine, creatine phosphokinase, TB levels. Among non-cirrhotic patients, 7 (17.5%) evolved to cirrhosis, 4 of them had withdrawn fibrate. One patient died 18 months after fibrate withdrawal and another one progressed to liver transplantation due to refractory itching despite the use of UDCA and ciprofibrate for 24 months.
Conclusion: Ciprofibrate appears to be as effective as other fibrates as adjunctive treatment of PBC. However, there were a large number of side effects. Randomized controlled trials are needed to compare the efficacy and safety of different fibrates.

FRI160

Utility of thiopurine metabolite testing in autoimmune hepatitis: defining an optimal therapeutic range for disease management and measurement may avert relapse and adverse drug reactions

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Background and Aims: Patients with autoimmune hepatitis (AIH) receive maintenance therapy with thiopurines, e.g. azathioprine (AZA) at 1–2 mg/kg/day. Genetic polymorphisms in the metabolism of AZA lead to variation in levels of metabolites, thioguanine nucleotide (TGN) and 6-methylmercaptopurine (6-MMP) which is associated with adverse drug reactions (ADR). For inflammatory bowel disease, a therapeutic range of TGN 235–450 pmol/8×10^8 erythrocytes has been identified to optimize effectiveness. We aim to elucidate the benefits of metabolite monitoring in patients with AIH.
Method: 109 patients with AIH were identified as having thiopurine metabolite levels between 1999–2019. In addition, 105 AIH patients on a weight-based dose of thiopurine, who had never had metabolite levels, were also identified. Charts were reviewed retrospectively. Chi squared test was used for statistical analysis.
Results: In those that had TGN monitoring, 73% (80/109) were female and the mean age at presentation was 35 yrs (range 4–82). In those that had no TGN monitoring, 74% (78/105) were female and the mean age at presentation was 37 yrs (range 7–70). In the TGN and non-TGN groups, 73% and 81% had type 1 AIH, 6% and 5% had type 2 AIH and 21% and 14% had auto-antibody negative AIH (respectively).
Patients with metabolite measurements had less loss of remission compared to those without metabolite levels (13% vs. 24%, p = 0.045). TGN levels within the therapeutic range predicted more stable

disease with fewer flares at 6 and 12 months post testing compared to patients with levels outside the therapeutic range (6 months: $p < 0.0001$; 1 year: $p = 0.0032$). Patients with normal TGN levels and normal TGN/6MMP ratio had more stable disease compared to patients with normal TGN levels and elevated TGN:MMP ratio ($p = 0.021$). High TGN:MMP ratios were related to more ADR compared to patients with normal TGN levels and TGN:MMP ratios ($p < 0.0001$). Average dose of AZA for patients in remission at 6 months post metabolite testing was 1.2 mg/kg/day. The remission group had an average baseline TGN level of 282 pmol/8 × 10^8 RBC (range 19–1009). The lowest number of ADR was observed in the group with subtherapeutic TGN levels. Interestingly, this group did not have the highest rate of relapse.

Conclusion: Measuring metabolite levels can help optimize treatment regimens in AIH patients with less ADR and relapses. It may be possible to define an alternative therapeutic range of TGN levels more specific to AIH.

FRI161

Correlation of serum bile acids and pruritus with aldafermin (NGM282) therapy in patients with primary sclerosing cholangitis

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Background and Aims: Pruritus is a common symptom in patients with cholestatic liver diseases, including PSC, an inflammatory and progressively fibrotic liver disease devoid of effective medical interventions. The pathogenesis of pruritus is poorly understood, and proposed pruritogens include bile acids (BA) and autotaxin/lysophosphatidic acid. Recently, BAs have been shown to activate the MRGPRX4 receptor located in the sensory neurons to induce itch. Aldafermin (NGM282), a non-tumorigenic FGF19 analogue, potently inhibited BA synthesis, improved hepatic inflammation, and decreased fibrosis markers in patients with PSC. To determine whether certain BA species may be related to pruritus, we correlated changes in individual serum BAs with patient-reported outcome measures of pruritus from a phase 2 aldafermin trial in patients with PSC.

Method: 62 subjects, with PSC by EASL criteria and an elevated ALP>1.5 × ULN at baseline (BL), were randomized to daily aldafermin 1 mg, 3 mg or placebo (PBO) for 12 weeks (W12). 5D-itch pruritus questionnaires (scores from 5 to 25) and fatigue severity numeric rating scale (NRS, from 0 to 10) were collected; higher numbers indicated more severe symptoms. Serum concentrations of BA species were determined by mass spectrometry. Scores were compared with the use of a mixed-effect model repeated measures analysis. Correlations between pruritus and serum BAs were assessed with a clinical anchor threshold of $r > 0.30$ and $p < 0.05$ as significant.

Results: At BL, pruritus severity by 5D-itch correlated with serum concentrations of GCA ($r = 0.35$, $p < 0.01$) and TCA ($r = 0.36$, $p < 0.01$), but not C4, GCDCA, TCDCA, ALP, ALT, AST or ELF. At W12, changes from BL were +0.6, 0, −1.3 for 5D-itch total score, −0.1, −0.2, −0.5 for pruritus direction, +0.1, −0.1, −0.3 for pruritus disability, 0.1, 0, −0.2 for pruritus degree, 0.5, 0.1, −0.1 for pruritus distribution, and 0, −0.4, −0.7 for fatigue NRS, in the PBO, 1 mg and 3 mg groups, respectively. Reductions from BL in GCA ($p < 0.001$) and GCDCA ($p < 0.001$) were observed in the aldafermin groups, but not in PBO. Change in pruritus severity from BL to W12 correlated with changes in GCA ($r = 0.39$, $p < 0.01$) and GCDCA ($r = 0.35$, $p < 0.01$). Change in fatigue severity did not correlate with BA levels.

Conclusion: Reductions in serum GCA and GCDCA correlated with reductions in 5D-itch score in PSC patients treated with aldafermin, suggesting that these BA species may serve as markers of pruritus response to aldafermin treatment.

FRI162

Higher prevalence of hepatitis E virus in autoimmune hepatitis: the role of false positive antibodies

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Background and Aims: Recent studies have found an increase in the seroprevalence of hepatitis E virus (HEV) infection in patients with autoimmune hepatitis (AIH) suggesting that the virus could play a role in the pathogenesis of the disease. However, the presence of false positive anti-HEV antibodies could explain the higher HEV seroprevalence observed in previous studies. Therefore, we aimed to assess the prevalence of positive anti-HEV IgM and IgG, and HEV-RNA in a cohort of patients with AIH, to determine the impact of positive HEV serology on patient outcome, and to evaluate the role of hypergammaglobulinemia and positive autoantibodies in the presence of positive anti-HEV serology.

Method: One hundred five patients tested for HEV infection (anti-HEV IgG, anti-HEV IgM and HEV-RNA) between 2014–2018 were included in the study: 50 with chronic AIH (more than 1 year on treatment), and 55 with an acute hepatitis (30 patients with acute AIH and 25 with non-autoimmune acute hepatitis). Clinical and laboratory data were analyzed.

Results: The seroprevalence of HEV infection was found to be higher in patients with acute AIH (17% vs. 10% in patients with chronic AIH and 8% in patients with non-autoimmune acute hepatitis). Only one patient from with the last group had HEV-RNA positive and was diagnosed with an acute HEV infection. Patients with acute AIH and positive anti-HEV IgG were older (58 vs. 40; $p = 0.006$), had higher IgG levels (27 g/dL vs. 13 g/dL; $p = 0.03$) and ASMA titres (1:160 vs. 1:80; $p = 0.045$), and were more likely to have another autoimmune disease (60% vs. 16%; $p = 0.03$). At the time of HEV testing, anti-HEV IgG positive patients had significantly higher serum IgG levels (17 g/L vs. 11 g/L; $p = 0.009$), ANA (1:160 vs. 1:60; $p = 0.026$) and ASMA titres (1:80 vs. 1:40; $p = 0.021$).

Conclusion: Despite the use of chronic immunosuppression, the seroprevalence of HEV infection in patients with AIH in Catalonia do not differ from that of the general population. The higher HEV seroprevalence in patients with acute AIH with higher levels of gammaglobulins and high antibody titres suggest the presence of cross-reactivity between HEV and liver antigens.

FRI163

Development and validation of a novel risk score predicting long-term survival in autoimmune hepatitis

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Background and Aims: No prognostic risk score is currently available to predict long term survival in autoimmune hepatitis (AIH) patients. The aim of this study was to develop and validate a risk score for AIH patients.
Method: The prognostic index was developed using uni- & multivariate Cox regression in a derivation cohort and validated in an independent cohort. A landmark analysis was used to assess biochemical remission as a baseline variable.
Results: In the derivation cohort 19 liver transplantations and 18 liver related death occurred in 396 patients (median follow-up 118 months; range: 1–560 months).
In multivariate analysis age (HR 1.023; p = 0.008), non-caucasian ethnicity (HR 2.633; p = 0.013), cirrhosis (HR 10.568; p < 0.001) and ALT level (HR 0.667; p = 0.010) were significant independent predictors for long term survival (C-statistic 0.866; 95% CI 0.822–0.910). In the validation cohort 39 of the 408 patients had liver transplantation or liver related death and median follow-up was 74 months (range: 1–496 months). Predicted 5-year event rate did not differ from observed event rate (high risk group 11.0% vs 10.4% (95% CI: 3.3%–17.0%); moderate risk group 1.3% vs 3.0% (95% CI: 0.0%–7.0%); low risk group 0.6% vs 3.4% (95% CI: 0.0%–8.0%); C-statistic 0.741 (95% CI 0.595–0.887)). Complete remission at 12 months after diagnosis was an additional independent predictor (HR 0.276; p = 0.040).
Conclusion: the newly developed prognostic index can predict long term survival free of liver transplantation and liver related death in AIH patients. Reaching biochemical remission within 12 months after diagnosis is the only identified modifiable independent risk factor.

FRI164
Safety and efficacy of temporary placement of fully covered metallic stent for dominant stricture among primary sclerosing cholangitis patients

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Background and Aims: when dominant stricture (DS) is diagnosed either prior to ERCP or during ERCP, there are multiple therapeutic options available to the endoscopist including dilation and stenting, each with their own benefits and drawbacks. The aim of the current study is to assess the safety and efficacy of fully-covered self-expandable metal stent (FCSEMS) in management of DS among PSC patients.
Method: we include PSC patients with refractory DS, defined as strictures resistance to conventional therapy (balloon dilatation, or and plastic biliary stent insertion) longer than three months. FCSEMS was placed for 3 months.
The primary outcome was the DS resolution at stent removal. And the secondary outcome was the DS recurrence as well as development of cholangitis, jaundice, and elevation of liver functions test and or refractory pruritus.
Results: 15 patient were enrolled between January 2016 to May 2018, FCSEMS was placed in all the 15 patients with DS, one patients need premature removal of the FCSEMS due to cholangitis on day 46 from the stent placement. Overall 14 patients complete planned 3 months, and after 90 days all the stents were softly removed.
The rate of DS resolution was, 43.7%. And recurrence occurred in 17.8 during median follow-up of 12 months. Improvement on liver function test, pruritus and weakness were observed in 28.5%, 57%, and 64.2% respectively. In all 14 patients MAYO score was improved by median 26%.
Adverse event was observed in 28.5% during 12 months follow-up, 1 case of cholangitis, 2 cases of biliary pancreatitis, 1 stent partially migrated to duodenum.
Conclusion: temporary FCSEMS was feasible, safe and effective treatment option among refractory DS PSC patients

FRI165
Understanding of central and peripheral fatigue in primary biliary cholangitis

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Background and Aims: Fatigue is the commonest symptom in patients with primary biliary cholangitis (PBC). It significantly impairs quality of life in approximately 20% of PBC patients (1, 2, 3). The pathogenesis of fatigue in PBC is multi-factorial and it is thought to be driven by both peripherally- and centrally-mediated processes. The aim of the study is to identify endotypes of fatigue in PBC to allow targeting of therapy in appropriate subgroups in future clinical trials of fatigue-modifying agents and approaches.
Method: Further analysis of data from patients from the UK-PBC Research Cohort recruited between 2008 and 2011. The PBC-40, Hospital Anxiety and Depression Scale (HADS) and Epworth Sleepiness Scale (ESS) assessment tools were used for symptoms assessment. Significant fatigue and significant cognitive symptoms were defined as moderate or severe symptoms using PBC-40 cut-offs. Symptom correlations between fatigue and cognitive symptoms were performed.
Results: There were 2002 patients included. 1203 (60%) had significant fatigue and 730 (36%) had significant cognitive symptoms. Of the 1203 patients with significant fatigue, 55% had significant cognitive symptoms; a combination we have named **"central-type fatigue."** The remaining patients with significant fatigue did not have significant cognitive symptoms and we named this group "**peripheral-type fatigue."** In central-type fatigue there was a strong linear association between fatigue and cognitive symptom severity ($p < 0.0001$, $r^2 = 0.22$) whilst the association was weak in peripheral-type fatigue. Patients with central-type fatigue were younger and experienced a greater level of perceived quality of life impairment, worse depression and worse sleep disturbance. Interestingly, significant cognitive symptoms without fatigue were very uncommon (3%) in our study but the converse was not true.

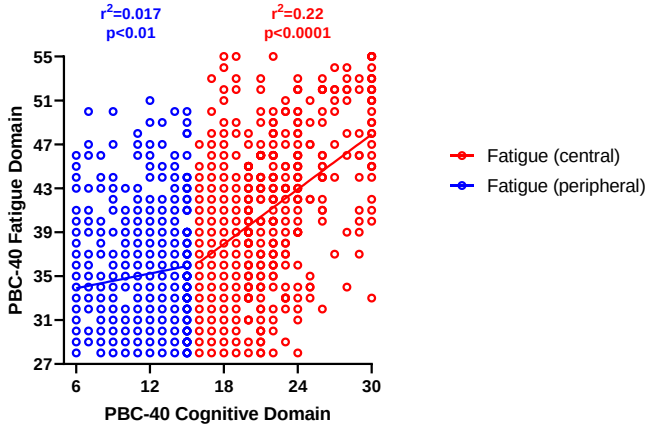

Figure: Correlation between cognitive and fatigue symptoms

Conclusion: The findings in the study have helped us to characterise fatigue endotypes in PBC. The strong association between the severity of cognitive symptoms and severity of fatigue in the subgroup of patients with the worst quality of life impairment suggests that the mechanisms underpinning the 2 symptoms are closely related. The greater impact on quality of life in those with central-type fatigue suggests that this group should be prioritized in future trials of symptom-modifying agents.

FRI166

Genetic variant c.711 in the hepatobiliary phospholipid transporter ABCB4 is associated with clinically relevant liver stiffness in chronic liver diseases

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Background and Aims: Liver scarring is a consequence of chronic liver diseases (CLD). Transient elastography (TE) threshold of 9.1 kPa has been recently demonstrated to have the best accuracy for the prediction of significant liver fibrosis (i.e. stages ≥F2, Serra-Burriel et al. *J Hepatol* 2019). The common *PNPLA3* (adiponutrin) p.I148M variant is associated with liver cirrhosis and carriers of the procholestatic *ABCB4* c.711T allele, who are also positive for the *PNPLA3* variant, might be at risk of progressive liver injury. Here, we investigate the relation between this common *ABCB4* polymorphism and liver stiffness as well as the interaction of both *ABCB4* and *PNPLA3* on fibrosis in a mouse model of chronic cholestasis (*Abcb4*$^{-/-}$ mice).
Method: n total, we investigated a cohort of 712 prospectively recruited patients with CLDs (278 women, age 50 ± 13 years) whose liver stiffness was measured non-invasively using TE. *ABCB4* and *PNPLA3* genotypes were determined by PCR-based assays. *Pnpla3* expression and liver injury were analysed in *Abcb4*$^{-/-}$ mice and wild-type controls.
Results: The frequency of the *ABCB4* c.711 minor allele in our cohort was 0.18. Median liver stiffness value was 6.7 kPa, and 226 individuals (32%) presented with TE ≥9.1 kPa. Carriers of the *ABCB4* variant presented significantly (P = 0.02, OR = 1.33) more frequently with liver stiffness ≥9.1 kPa. In a multivariate regression model including the *ABCB4* variant (P = 0.047, OR = 1.43) as well as non-genetic profibrogenic factors such as BMI (P = 0.043, OR = 1.04) and age (P < 0.01, OR = 1.02), all proved to be independent risk factors for fibrosis stage ≥F2. *Abcb4* knockout in mice led to enhanced liver injury (reflected by increased *Col1a2* expression and elevated collagen contents), which was coupled with significantly (P < 0.05) lower hepatic expression of *Pnpla3* as compared to wild-type mice.
Conclusion: The procholestatic *ABCB4* c.711T allele might represent a new genetic risk factor for clinically relevant liver fibrosis. Lower expression of adiponutrin in fibrotic livers of *Abcb4*$^{-/-}$ mice alludes to the interaction between altered phospholipid metabolism and *PNPLA3* in progressive liver injury. Our results suggest that *Abcb4* knockouts might represent a model to further dissect the role of *PNPLA3* in liver fibrosis.

FRI167

Response to treatment in autoimmune hepatitis determines the health-related quality of life

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Background and Aims: Autoimmune hepatitis (AIH) is a rare chronic liver disease resulting from inflammation and eventual destruction of hepatocytes. Incomplete response to treatment can lead to disease progression and end-stage liver disease. Frequently the health-related quality of life (HRQL) is impaired in AIH. In this prospective study we assessed the impact of the response to treatment on HRQL using the validated chronic liver disease questionnaire (CLDQ) in AIH.
Method: A total of 116 patients with AIH (n = 89) or AIH/PSC/PBC overlap (n = 27) were prospectively enrolled in this study at an outpatient hepatology clinic in Germany starting in July 2018. The CLDQ was used to assess HRQL and clinical and laboratory assessment was performed at baseline. The CLDQ is a validated tool and reports a scale from 1 to 7, with 1 indicating worst and 7 indicating best HRQL in five domains and a total score.
Results: The mean CLDQ overall score was 5.3 ± 1.3 with the lowest score in the subscale fatigue (4.3 ± 1.7) and the highest score for activity (5.8 ± 1.3). The score for activity was significantly lower in female than in male (5.7 ± 1.4 vs. 6.4 ± 0.9; p < 0.05). Patients with a complete response to immunosuppressive therapy defined as normalization of ALT, AST and IgG had a significantly higher CLDQ overall score compared to patients with incomplete response, respectively (5.7 ± 1.2 vs. 5.1 ± 1.3; p < 0.05). The scores of the subscales abdominal symptoms (6.1 ± 1.4; p < 0.05), activity (6.2 ± 1.2; p < 0.05), emotional functioning (5.44 ± 1.40; p < 0.05) and worry (5.8 ± 1.5; p < 0.05) were also significantly higher in patients with complete response. Interestingly, the subscale fatigue, which showed the lowest score overall, was independent of treatment response (4.7 ± 1.6 vs. 4.1 ± 1.7; p = 0.104). There was a negative correlation between the level of gGT and the CLDQ total value (r = –0.276; p < 0.01). A negative correlation was also observed for other cholestatic parameters including bilirubin and ALP with the subscales fatigue (bilirubin: r = –0.218; p < 0.05), systemic symptoms (ALP: r = –0.241; p < 0.05) and activity (ALP: r = –0.222, p < 0.05).
Conclusion: Overall, AIH is associated with a high symptom burden. A complete response to treatment is associated with a significant higher HRQL. In addition, cholestatic patterns of liver injury showed a negative impact on the subscales symptoms and activity of the CLDQ. Achieving a complete treatment response will therefore be beneficial for all aspects of relevance – feeling, function and survival.

FRI168

Serum bile acid species are associated with liver fibrosis and clinical disease progression in patients with primary sclerosing cholangitis

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Background and Aims: PSC is a cholestatic disorder characterized by abnormal serum bile acid (BA) levels, but there are limited data regarding individual BA species. Our aim was to evaluate associations

between BA species, liver histology, and disease progression in patients with PSC.

Method: Levels of 15 BAs and the BA intermediate, 7α-hydroxy-4-cholesten-3-one (C4), were quantified by LC-MS/MS (Agilent 1290/Sciex, Metabolon) in fasting serum samples from patients with compensated large-duct PSC at baseline (BL) in a 96-week, phase 2 trial of simtuzumab (NCT01672879). Ursodeoxycholic acid (UDCA) and conjugates were removed as potential confounders in this analysis. Fibroblast growth factor 19 (FGF19) was measured by ELISA in fasting plasma samples and liver fibrosis at BL was staged according to the Ishak classification. Associations between BA species, Ishak fibrosis stage, and clinical parameters (e.g. liver biochemistry, Enhanced Liver Fibrosis [ELF] test), as well as their prognostic utility for PSC-related events (e.g. decompensation, cholangitis, transplantation) and progression to cirrhosis were determined.

Results: 115 patients were included (mean age 44 yrs, 62% male, 59% with IBD, 63% on UDCA, 54% with advanced [Ishak F3-F6] fibrosis). Median total BAs at BL were 2383 ng/mL (IQR 1204, 7406); conjugated primary BAs (glycocholic acid [GCA], taurocholic acid [TCA], glycochenodeoxycholic acid [GCDCA], and taurochenodeoxycholic acid [TCDCA]) contributed to more than 70% of the total BA pool. Total and primary BAs were highly correlated with ELF and its components (Spearman $\rho = 0.56–0.71$), serum ALP ($\rho = 0.58–0.60$), ALT ($\rho = 0.57–0.60$), and direct bilirubin ($\rho = 0.68–0.71$), and Ishak fibrosis stage ($\rho = 0.51$; all $p < 0.05$), while correlations between secondary BAs and these markers were weaker ($|\rho| < 0.20$). Compared with patients with no to mild (F0-F2) fibrosis, those with advanced fibrosis (F3-F6) had higher total (1537 vs 4313 ng/mL [$p < 0.001$]; AUROC 0.77) and primary BAs (1245 vs 4100 ng/mL [$p < 0.001$]; AUROC 0.77), and lower C4 (13.7 vs 6.46 ng/mL [$p < 0.001$]; AUROC 0.69). Levels of all four conjugated primary BAs were significantly higher in patients with advanced fibrosis (all $p < 0.001$, AUROCs 0.76–0.79). By week 96, 23 patients (20%) developed a PSC-related event (cholangitis, n = 15; jaundice, n = 4; cholangiocarcinoma, n = 1; decompensation, n = 3). Higher BL total BAs, primary BAs, GCA, GCDCA, TCA, and TCDCA, but not secondary BAs, FGF19, or C4, were associated with an increased risk of PSC-related events (Table). Similar factors predicted progression to cirrhosis (15%).

Table: Associations between baseline BAs, C4, and FGF19 with PSC-related clinical events

Marker	With PSC-Related Event (N=23)	Without PSC-Related Event (N=92)	Wilcoxon P-value	Hazard Ratio[§] (95% CI)	HR P-value
Total BAs*	4152.87 (2392.37, 10096.84)	2148.8 (1082.29, 6579.8)	0.0083	1.39 (1.06, 1.81)	0.017
Total primary BAs	3357.39 (2131.78, 10074.4)	1810.84 (774.37, 5354.4)	0.0076	1.36 (1.06, 1.74)	0.014
Total secondary BAs*	338.7 (109.63, 771.9)	259 (126.29, 630.89)	0.793	1.03 (0.76, 1.39)	0.866
GCA	1140 (503, 3180)	498 (157, 1515)	0.012	1.36 (1.07, 1.72)	0.012
GCDCA	1090 (689, 3330)	725.5 (356, 1870)	0.028	1.4 (1.05, 1.86)	0.021
TCA	476 (225, 1540)	106 (29.8, 594)	0.002	1.29 (1.08, 1.54)	0.004
TCDCA	421 (244, 1180)	182 (53.7, 661)	0.006	1.33 (1.08, 1.62)	0.007
FGF19	99 (70, 214)	111 (61, 177)	0.928	1.34 (0.82, 2.19)	0.247
C4	10.6 (3.0, 15.5)	11.9 (5.4, 23.8)	0.168	0.74 (0.49, 1.12)	0.159

Unless indicated, data are median (Q1, Q3) and measurement units are ng/mL.
* UDCA and conjugates removed from total and secondary BAs.
§ Hazard ratio from Cox proportional hazards model for PSC-related clinical event-free survival based on log-transformed marker.

Conclusion: In patients with compensated PSC, total serum BAs, as well as conjugated primary BAs, are markers of liver fibrosis and predict clinical disease progression. These data support ongoing evaluation of therapies that reduce BA levels (e.g. FXR agonists) for the treatment of PSC.

FRI169

Removal of fibrosis-related genes identifies a hepatic gene expression signature that identifies canonical signaling pathways and is correlated with clinical outcomes in patients with primary sclerosing cholangitis

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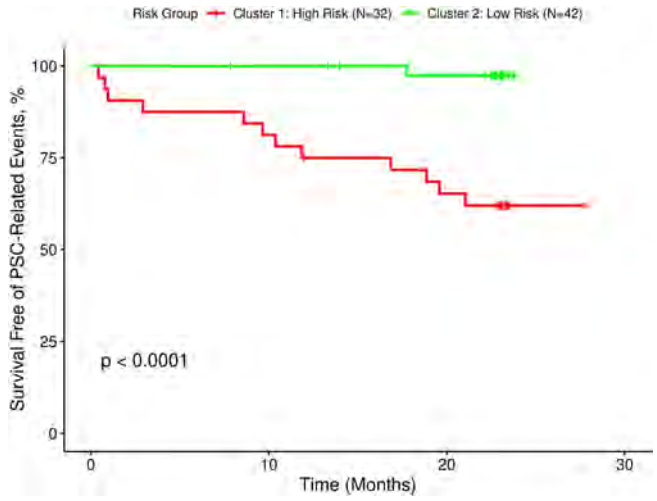
Background and Aims: Primary sclerosing cholangitis (PSC) is a heterogeneous cholangiopathy that leads to progressive biliary fibrosis. In this study, RNA sequencing (RNA-Seq) of liver tissue from PSC patients was performed to identify associations between biological pathways and clinical events independent of fibrosis stage.

Method: RNA-Seq (SureSelect protocol) was performed on baseline FFPE biopsies from 74 PSC patients enrolled in a 96-week clinical trial (NCT01672853). RNA quality was assessed by DV200 and gene expression quantified using Salmon. A semi-supervised approach was used to identify in-tissue, fibrosis-independent gene expression signatures associated with time to first PSC-related clinical event (e.g. cholangitis, decompensation, cholangiocarcinoma). The effect of fibrosis was subtracted from gene expression using the "removeBatchEffect" function in R package limma. Patient clustering, using genes associated with clinical events as input, was carried out using Consensus Clustering algorithm. Differential expression based on the identified risk groups was performed by Limma-Voom and pathway analysis by Ingenuity Pathway Analysis (IPA). All P-values were corrected for multiple testing.

Results: The median age was 48 yrs, 71% were male, 49% had IBD, 68% were prescribed UDCA, and 44% had Ishak F3-F6 fibrosis. The first principle component of RNA-Seq data accounted for 18% of variance and correlated with fibrosis stage ($\rho = –0.80$; $P < 0.001$). After removing the effect of fibrosis on gene expression data, PC1 was no longer associated with fibrosis ($\rho = –0.19$; $P = 0.11$). The patient clustering approach identified two distinct PSC patient clusters with differential risk of time to first PSC-related clinical event (log-rank $P < 0.0001$; Figure). These PSC patient clusters were not significantly different in terms of fibrosis stage ($P = 1.0$), enhanced liver fibrosis score ($P = 0.25$), hepatic α-SMA expression ($P = 0.87$), or serum concentrations of ALP ($p = 0.48$), ALT ($p = 0.97$), or GGT ($p = 0.74$). The top pathways identified by IPA were eIF2 signaling and regulation of eIF4/p70S6K signaling. Genes involved in the unfolded protein response (UPR), *ATF6* and *eIF2*, were among the transcripts differentially expressed between the PSC clusters (down-regulated in the high-risk group by log-fold-changes of –0.18 [$P = 0.02$] and –0.16 [$P = 0.02$], respectively).



Conclusion: After removing the influence of fibrosis-related pathways, this hepatic transcriptomic analysis identified canonical biological pathways, such as the UPR, that are associated with prognosis in PSC.

FRI170

Hepatic transcriptomic analysis identifies a mast cell gene expression signature that correlates with fibrosis stage and is prognostic in patients with primary sclerosing cholangitis

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Background and Aims: PSC is a heterogeneous cholangiopathy of unclear pathogenesis. Experimental and clinical data suggest roles for mast cell infiltration and senescence in the pathogenesis of PSC. We hypothesized that a mast cell gene expression profile would be increased in advanced PSC and explored associations with senescence-related gene expression.

Method: RNA sequencing (RNA-Seq, SureSelect protocol) of baseline FFPE liver biopsies from 75 patients with PSC enrolled in a clinical trial (NCT01672853) was performed to identify mast cell (Nakajima) and senescence (Reactome; both Broad Institute, GSEA C2 collection) gene expression signatures. RNA quality was assessed by DV200 and gene signature expression was quantified using a modified z-score approach (Plage method). Associations between these gene expression signatures and fibrosis stage, clinical parameters (e.g. IBD, UDCA use, liver biochemistry, ELF score, serum IL-8 and total bile acids, pruritus by Visual Analog Scale), and PSC-related clinical events (e.g. cholangitis, decompensation, cholangiocarcinoma) were evaluated.

Results: The median age was 48 yrs, 71% were male, 49% had IBD, 68% were on UDCA, and 44% had bridging fibrosis or cirrhosis (Ishak stages F3-F6). The mast cell gene expression signature was associated with increasing fibrosis stage (Figure) and correlated with ELF score (Pearson r = 0.63; p < 0.001), serum alkaline phosphatase (r = 0.44; p < 0.001), ALT (r = 0.36; p = 0.002), bilirubin (r = 0.40, p < 0.001), IL-8 (r = 0.39, p < 0.001), and total serum bile acids (r = 0.54, p < 0.001) but not IBD status, UDCA use, or pruritus severity. A significant inverse correlation was observed between the mast cell and senescence-related signatures (r = –0.90; p < 0.001), which contain no common genes. During a median follow-up of 23 months, 14 patients (19%) had a PSC-related event. In univariate Cox regression analysis, higher scores (≥the median) for the mast cell signature (hazard ratio [HR] 2.62; 95% CI 0.92, 7.49) and lower scores (< the median) for the senescence signature (HR 5.06; 95% CI 1.76, 14.51) were associated with an increased risk of events.

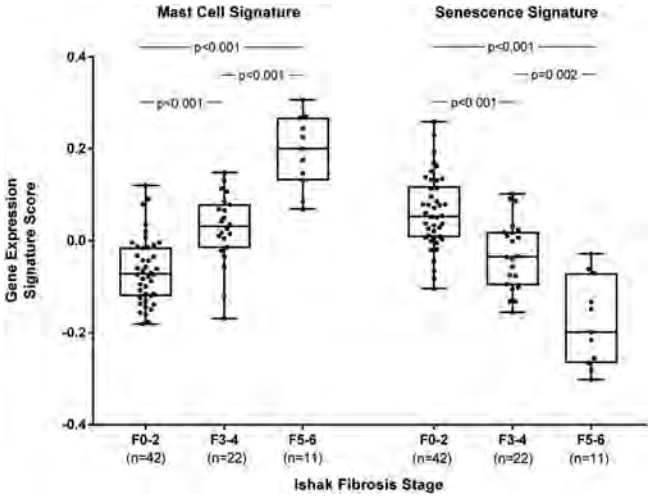

Figure: Associations Between Mast Cell and Senescence-Related Hepatic Gene Expression Signatures and Ishak Fibrosis Stage in PSC.

Conclusion: In patients with PSC, hepatic expression of mast cell-related genes is associated with increasing fibrosis stage, is prognostic, and is inversely correlated with expression of senescence-related genes. These data support experimental findings that suggest inhibition of mast cell infiltration and activation as potential therapeutic targets in PSC.

FRI171

Simultaneous liver and spleen stiffness measurements as complementary methods for fibrosis quantification in autoimmune hepatitis

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Background and Aims: Liver stiffness measurement (LSM), commonly performed using transient elastography (TE), is widely applied to assess liver fibrosis, but results can be biased by active hepatitis. This bias might be lower in spleen stiffness measurement (SSM), however, there is limited data concerning SSM in patients with autoimmune hepatitis (AIH). Here, we compare LSM-SWE and SSM-SWE (both performed by 2D-shear wave elastography) to LSM-TE and liver biopsy (LB) in prospectively recruited patients with AIH.

Methods: At first, LSM-SWE and SSM-SWE were compared to LSM-TE in 90 patients (80% women, median age 31 years, 21% with liver cirrhosis) treated for AIH for ≥6 months. Then, SWE and LB were performed in 57 patients with AIH (77% women, median age 37 years, 60% therapy-naïve, 37% with liver cirrhosis, 44% with histological signs of flare), with a median interval of 12 days between procedures.

The optimal SWE cut-offs were calculated in relation to fibrosis stages according to Batts & Ludwig. Finally, SWE changes during 18 months follow-up were evaluated in a cohort of 74 outpatients with AIH (80% women, median age 37 years, 28% with cirrhosis).

Results: LSM-SWE and SSM-SWE strongly correlated with LSM-TE ($P < 0.001$), however LSM-SWE was superior ($P < 0.01$) to SSM-SWE in identifying cirrhosis in treated patients. LSM-SWE and SSM-SWE correlated significantly ($P < 0.001$) with fibrosis in LB ($r = 0.74$, $r = 0.79$, respectively), but only LSM was associated with histopathological inflammatory score ($r = 0.39$, $P < 0.05$). When compared to LB, the optimal cut-offs for cirrhosis by LSM-SWE and SSM-SWE were 16.1 kPa (AUROC 0.92, $P < 0.001$, PPV = 0.76, NPV = 0.94) and 29.8 kPa (AUROC 0.95, $P < 0.001$, PPV = 0.88, NPV = 0.94), respectively. During follow-up, substantial improvements of LSM-SWE, ALT, and MELD (all $P \leq 0.01$), but neither of SSM-SWE nor markers of portal hypertension (PLT and PLT-to-spleen ratio) were detected. In subgroup analysis of patients with flares at baseline ($n = 14$) a significant ($P < 0.005$) reductions of LSM-SWE, SSM-SWE, and MELD was noted.

Conclusions: LSM-SWE and SSM-SWE might serve as complementary tools for the assessment of cirrhosis in patients with AIH. In patients with AIH flare and active hepatitis, SSM-SWE might provide more accurate estimation of liver fibrosis as compared to LSM-SWE alone.

FRI172

Pregnancy outcomes for women with primary sclerosis cholangitis and primary binary cholangitis

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Background and Aims: To determine maternal, obstetric and neonatal outcomes in a cohort of women with primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC)

Method: Retrospective cohort study of 10 UK specialist centres managing pregnant women with liver disease. Women with a diagnosis of PBC and PSC and a pregnancy of ≥20 completed weeks' gestation were included. Adverse outcomes were defined as maternal: development of ascites, variceal bleeding, encephalopathy and jaundice; obstetric events: gestational hypertension, pre-eclampsia and postpartum haemorrhage; and neonatal: stillbirth, preterm delivery, and admission to neonatal unit. The relationship of alanine transferase (ALT) and bile acid levels with gestation at delivery was studied.

Results: The first recorded pregnancies of 34 women with PSC and 27 with PBC were analysed. There were 60 livebirths and one intrapartum stillbirth that did not occur in the context of maternal cholestasis. Overall median gestation of delivery was 38 weeks, but the rate of preterm birth was 28% (17/61 deliveries) of which 76% (13/17) were spontaneous. Gestation at birth negatively correlated with maternal serum ALT concentration at booking ($p = 0.017$) and serum bile acid concentration during pregnancy ($p = 0.016$). There were no other significant correlations and maternal and neonatal outcomes were good.

Conclusion: Pregnancy in PBC and PSC is well tolerated, but women should be counselled regarding the increased risk of preterm birth. Measurement of maternal ALT and bile acids may help identify women at risk of preterm delivery.

FRI173

Machine learning models accurately interpret liver histology and are associated with disease progression in patients with primary sclerosing cholangitis

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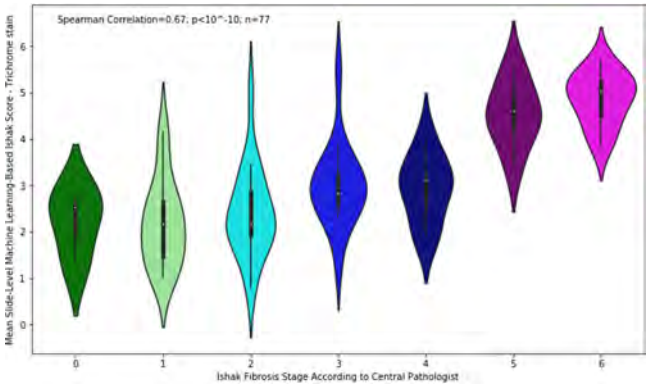
Background and Aims: Variability in histological evaluation in patients with PSC may hinder disease staging and confound clinical trial results. Our aim was to develop machine learning (ML) models to accurately and automatically interpret PSC histology.

Method: ML models were developed using whole slide images of biopsies from 141 PSC patients enrolled in a trial of simtuzumab. Fibrosis was staged at baseline (BL) and weeks 48 and 96 by a central pathologist (CP) according to the Ishak classification using trichrome (TC)-stained slides. Using an ML platform (PathAI, Boston, MA), convolutional neural networks (>20 layers and 8 million parameters) developed for NASH (Pokkalla, AASLD 2019) were further trained using 44,000 annotations (eg. fibrosis, lobular/portal/interface inflammation, bile ducts/ductules) from 29 board-certified pathologists on images from 252 H&E, 254 TC, and 330 picrosirius red (PSR)-stained slides. The model was trained to recognize and summarize these features at slide-level. For fibrosis, models were trained on TC and PSR images using slide-level CP Ishak stages to recognize patterns associated with each stage. These region-based scores were used to generate a slide-level ML fibrosis score. Correlations between these scores and CP-derived fibrosis stage were evaluated on test images excluded from model training (77 TC, 88 PSR), and associations between ML-derived features with clinical parameters, PSC-related events (e.g. decompensation, cholangitis, transplantation), and progression to cirrhosis were determined.

Results: ML fibrosis scores were strongly correlated with Ishak stage by the CP ($\rho = 0.67$ [PSR and TC images]; both $p < 10^{-10}$; Figure), serum ELF ($\rho = 0.68$–0.72; both $p < 10^{-11}$), and serum alkaline phosphatase (ALP) ($\rho = 0.49$–0.56; both $p < 10^{-5}$). During a median follow-up of 23 months (IQR 18.9, 23.1), 21% of patients (29/141) developed a PSC-related event. Events were associated with higher ML Ishak fibrosis score at BL (HR per unit: 1.74 [95% CI 1.18, 2.59]) and greater area of interface inflammation and remodeling (HR per 1%: 1.39 [95% CI 1.14, 1.70]) (both on TC images). Discrimination of the ML Ishak fibrosis score (TC) was similar to CP-derived Ishak stage, ELF, and serum ALP (c-statistics 0.68–0.69), and area of interface inflammation and remodeling (c-statistic 0.65). The ML Ishak fibrosis scores were also predictive of progression to cirrhosis at week 48 or 96 (AUROCs 0.86 for TC and 0.76 for PSR). By comparison, AUROCs for CP-derived Ishak stage, ELF, and ALP were 0.73, 0.81, and 0.74, respectively.



Conclusion: ML models demonstrated high concordance with pathologist assessment of PSC-related fibrosis, and ML-derived metrics were associated with the risk of disease progression. These data highlight the potential of ML for automated and quantitative assessment of liver histology and risk stratification in PSC.

FRI174

CCL24 modulates fibrosis development in primary sclerosing cholangitis: correlation of human serum CCL24 levels with fibrosis markers and data from the Mdr2−/− mouse model.

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Background and Aims: Primary sclerosing cholangitis (PSC) is a disease involving hepatic inflammatory, cholestatic liver damage and fibrosis, with no approved medical treatment. CCL24, a chemokine that was shown to be involved in the development of liver inflammation and fibrosis in several animal models is over expressed in liver biopsies of PSC patients. Blocking CCL24, was shown to diminish liver fibroblast activation and reduce liver fibrosis in both NASH and PSC models. Here we aim to study the correlation between CCL24 and fibrotic biomarkers in serum of PSC patients and to assess the anti-fibrotic effect of blocking CCL24 in the MDR2−/− mouse model.
Method: Serum CCL24 levels of PSC patients was quantified by ELISA and corelated with the serum levels of the fibrotic biomarkers TIMP-1 and ELF scoring. Cholestatic liver injury and fibrosis were studied in C57/bl MDR2−/− mice treated with either placebo or 5 mg/kg of the CCL24 blocking antibody CM-101(D8) by SC injections. Serum alkaline phosphatase (ALP) and bile acid (BA) levels were measured and fibrosis was evaluated by histopathological analysis of H&E and Sirius red stained liver sections. Expression of liver TIMP-1 and Col1a1 were tested by Real-time PCR.
Results: MDR2−/− mice developed severe ductular reaction accompanied by progressive fibrosis. CM-101 (D8) treatment diminished cholestatic injury manifested in normalization of ALP and significant reduction of BA levels (144 ± 15 vs.173 ± 27; $p \leq 0.05$ and 15 ± 7 vs. 34 ± 13, $p \leq 0.001$, respectively). Histological assessment of fibrosis by Sirius red staining revealed that CM-101(D8) treatment significantly attenuated fibrosis development. This was further supported by reduced liver expression of the profibrotic genes Col1a1 and TIMP-1. CCL24 levels in serum from PSC patients were corelated with serum levels of TIMP-1 ($R = 0.65$, $p \leq 0.005$), and ELF score ($R = 0.39$, $p = 0.06$) suggesting an association between CCL24 and PSC related fibrosis.

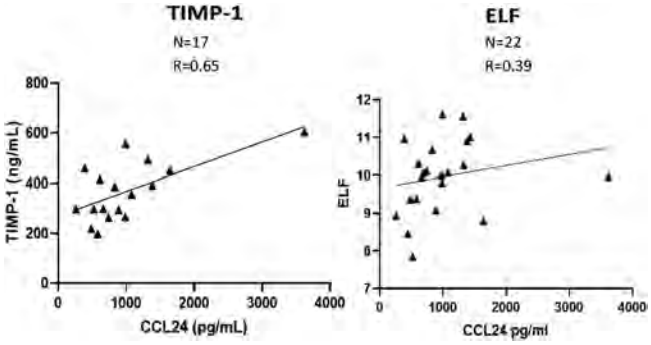

Figure: Correlation of CCL24 with fibrotic biomarkers in PSC patients.

Conclusion: CCL24 expression correlates with increased expression of TIMP-1 and ELF scoring in the serum of PSC patients. CCL24 blockade using CM-101(D8), a specific anti-CCL24 antibody, in an animal model of cholestasis, reduced TIMP-1 and Col1a1 expression in the liver reflecting significant attenuation of hepatic fibrosis. These findings support the potential of CCL24 as a therapeutic target in liver fibrotic diseases and the anti-fibrotic activity of CM-101.

FRI175

Belimumab: a promising third line treatment option for refractory autoimmune hepatitis

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Background and Aims: Autoimmune hepatitis (AIH) is an autoimmune liver disease of unknown aetiology that may lead to end stage liver disease if untreated. In real world conditions, however, it appears that less than 50% of patients achieve complete response on standard immunosuppression. Serum B cell activating factor (BAFF) levels are high in AIH patients contributing probably to disease pathogenesis. As belimumab, a BAFF inhibitor, was proved effective in other autoimmune diseases, the aim of the present case-study was to investigate the safety and efficacy of belimumab as a third line treatment option in patients with AIH refractory to standard treatments.
Method: Belimumab (10 mg/kg iv) was administered as add on, third line treatment in two AIH patients who had partial response and multiple flares with conventional regimens. Belimumab was administered on days 0, 14, 28 and every 28 days thereafter according to previous publications. The outcome after 12 months of treatment was evaluated.
Results: Both patients (27 years old female and 58 years old male) had AIH-related compensated cirrhosis at diagnosis. The female patient had received treatment with prednisolone (PRED, 1 mg/kg/d) and azathioprine (AZA, 1.5 mg/kg/d) for 12 months during which she suffered multiple relapses and then mycophenolate mofetil (MMF, 2 g/d) for 54 months with partial response. The male patient received combination therapy with PRED and AZA for a short period due to severe myelotoxicity and then MMF for 46 months with initial complete response but flares in any attempt of PRED withdrawal. Therefore, add on third line therapy with belimumab was initiated at month 66 and 47 of follow-up. Both patients achieved complete response after the 1st and 5th belimumab infusion, respectively, and remained in remission during the next 12 and 8 months, respectively, while receiving low corticosteroids dose (<10 mg/d). Of interest, in the female patient sequential liver stiffness measurements were improved (from 14.6 kPa to 9 kPa) while second liver biopsy showed significant improvement (no inflammatory activity and moderate

fibrosis). No adverse events were observed and none of patients decompensated.
Conclusion: Belimumab could be an effective and safe third line treatment option for patients with refractory AIH and advanced liver fibrosis. However, long-term randomized control trials are needed in order to assess belimumab efficacy and safety in this difficult to treat subgroup of AIH patients.

FRI176
European Association for the Study of the Liver primary biliary cholangitis guideline clinical care standards: the patient experience as recorded by PBC Foundation app and International Patient Registry
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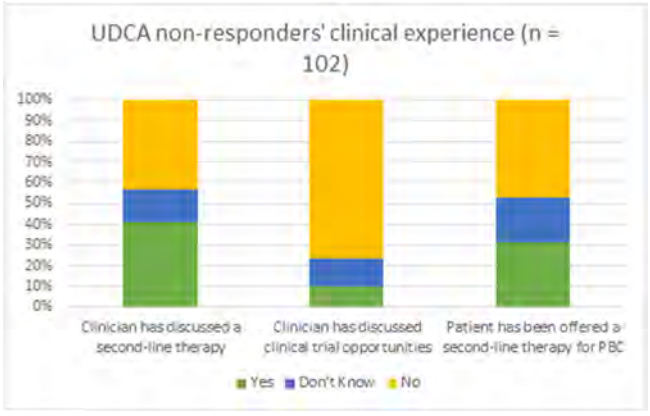
Background and Aims: In 2017, EASL published practice guidelines for care in Primary Biliary Cholangitis (PBC), and set out clinical care standards. Using the PBC Foundation's smartphone App, linked to an international patient registry, we aimed to assess the patient experience, particularly in reference to the EASL clinical care standards. We focussed on ursodeoxycholic acid (UDCA) dose, response status, second-line therapy and symptoms.
Method: PBC Foundation's self-management App became available to use in May 2019. To date, the App has been downloaded by over 2500 service users. A survey was produced via the App, inviting patients to answer a series of "radio-style" questions, with only tick box options to answer. Members were invited to the survey in Oct 2019. Only patients with PBC were included.
Results: 153 patients with PBC (N = 153) responded to the survey. As compared to EASL's target of 90%, only 51% of respondents (n = 78) were on optimal UDCA dose (13–15 mg/kg/day). 18% (n = 28) received higher doses (>15 mg/kg/day). Short of EASL's target of 90%, only 66.7% respondents (n = 102) reported that their clinician had asked them about their PBC symptom burden in the last 12 months.



EASL set a target of 80%, yet only 62% respondents (n = 95) had been informed of their UDCA response status by their clinicians.
Of the 153 respondents, 102 (66.6%) were UDCA non-responders. Of these only 41.2% (n = 42) reported their clinicians had discussed second-line therapies with them and 15.7% (n = 16) reported they did not know. Only 31.4% (n = 32) had been offered a second-line therapy by their clinicians, with a further 21.6% (n = 22) not knowing if they had been offered a second-line therapy
Overall, 75.5% (n = 77) reported their clinician had not spoken to them about clinical trial opportunities with only 9.8% reporting such a discussion with their clinicians.

Conclusion: The PBC App is an effective way to capture treatment related information with a high level of patient engagement. The results of this survey are well below the clinical care standards proposed in the EASL PBC guidelines. Our study highlights the need for improved clinician education about the current best practice in the care and management of PBC.

FRI177
A multi-disciplinary approach to igG4 related disease aids in diagnosis and management
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Background and Aims: IgG4-related disease (IgG4-RD) is a complex multi-system fibro-inflammatory disorder that often manifests as autoimmune pancreatitis or sclerosing cholangitis. Challenges include diagnostic differentiation from malignancy and other inflammatory conditions, careful management to minimise gluco-corticoid-induced toxicity and prevention of progressive organ dysfunction. We describe the experience of the first multi-site specialist IgG4-RD multi-disciplinary meeting (MDM) incorporating a broad range of generalists and specialists and held via web-link between Oxford University Hospitals and University College London Hospital.
Method: Data from the IgG4-RD MDM was collected prospectively in real-time over a three-year period. We performed a review of patient electronic records with specific emphasis on diagnosis, management decisions and outcomes.

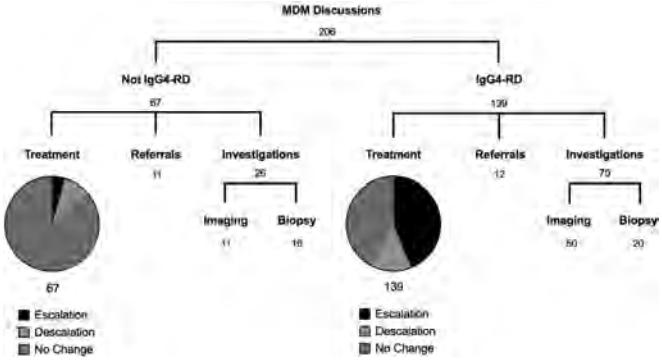

Figure 1: IgG4 MDM management recommendations.

Results: Over three-years, there were 206 discussions on 156 patients. Of these patients discussed, 97 (62%) were considered to have definite (60) (meeting defined diagnostic criteria) or possible (37) (considered most likely diagnosis at MDM) IgG4-RD. 67% had multi-organ involvement and 23% had a normal serum IgG4. Disease phenotype of these IgG4-RD patients was as follows: Systemic 47.4%, Hepatopancreatobiliary 37.1%, Ear Nose & Throat 12.4% and Retroperitoneal/Aortic 3.1%. The average number of specialist opinions sought prior to MDM was four. Management was changed in the majority of patients (74%) with the MDM recommending treatment escalation in 61 cases, including 19 recommendations for rituximab (Figure 1).
Conclusion: Our cross-discipline IgG4-RD MDM enhanced diagnostic clarity, a major concern for patients who may experience delays and misdiagnosis, often compounded by cross-speciality presentation of a rare disease. The pooled experience of our MDM provided consistency in complex decisions including management of multi-

system or sub-clinical disease. Our MDM based approach could be used as a model for IgG4-RD management at other centres.

FRI178

Long-term prevalence of gastro-oesophageal varices in early primary biliary cholangitis patients with good response to treatment

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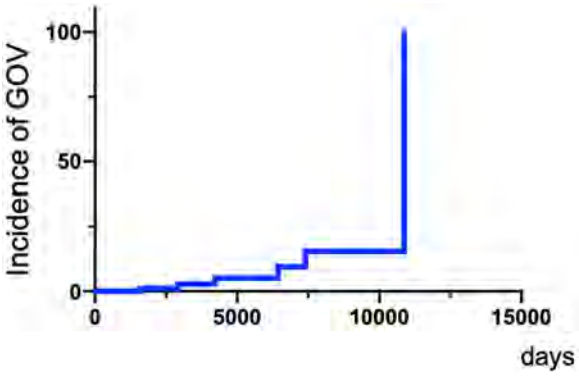
Background and Aims: Recent routine testing for anti-mitochondrial antibodies has increased the number of patients with early primary biliary cholangitis (PBC). Furthermore, most PBC patients respond to ursodeoxycholic acid, leading to good prognosis and an increased number of aged PBC patients. Since Gastro-oesophageal varices (GOV) is a life-threating complication in chronic disease patients, several clinical tools for the prediction of varices in chronic liver disease patients have been developed. However, in PBC patients, risks related to development of varices are still obscure. We sought to determine the long-term prevalence and clinical characteristics of GOV in PBC patients

Method: We retrospectively reviewed 392 PBC patients who had undergone oesophago-gastro-duodenoscopy (OGD) regularly from 1985 to 2018. Histopathological data were available in 160 patients. We divided the patients into two groups and explored the characteristics of patients with varices; early stage (Scheuer I and II) and advanced stage (Scheuer III and IV).

Results: Fifteen percent (59/392) of patients had GOV. Twenty-six patients had GOV at the time of diagnosis, and 32 patients developed GOV during the course. The median follow-up period was 7.1 years prior to the development of GOV. Multivariate analysis revealed that itching, reduced serum albumin level and decreased platelet count were significantly associated with GOV development. In histopathological analysis, advanced-stage PBC patients showed significantly higher incidence of GOV than early stage PBC ($p < 0.0001$, log-rank test). From the viewpoint of response to treatment, patients who had good response to UDCA and met Paris criteria showed significantly lower prevalence of GOV ($p < 0.0001$, log-rank test). Patients with GOV had a significantly higher GLOBE score than those without GOV (0.89 ± 0.30 vs. -0.06 ± 0.63, $p = 0.0006$). On the other hand, among early Scheuer stage PBC patients who met Paris criteria, 5.7% (6/105) of patients developed GOV during the long-term follow up (1.1–29.1 years, Figure). Laboratory findings in those patients were comparable to the early stage PBC patients without GOV.



Conclusion: Early PBC patients with good response to UDCA treatment can develop GOV. Since it's difficult to predict the development of GOV in early PBC patients, we should bear in mind that periodic endoscopic screening for varices is important even in steady PBC patients.

FRI179

Symptom burden in patients living with primary biliary cholangitis: indigenous Canadians report significantly higher PBC-40 quality of life scores

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Background and Aims: Primary Biliary Cholangitis (PBC) is a chronic liver disease that adversely impacts quantity and quality of life. We aimed to investigate differences in PBC-related quality of life by ethnicity in our multicentre Canadian cohort using the UK-derived PBC-40 questionnaire.

Method: The Canadian Network for Autoimmune Liver disease (CaNAL) is a multicentre registry including patients with PBC followed prospectively. Mixed-effects regressions with random intercepts were used to investigate the association of PBC-40 quality of life scores with ethnicity, in participants who completed at least one PBC-40 quality of life questionnaire.

Results: 318 patients were included from 5 centres in Canada with a mean of 1.2 measurements per patient. Mean (SD) age at first PBC-40 questionnaire was 59.4 (10.3) years, 94% (n = 299) were female, and mean duration of disease was 9.4 (7.7) years. 82% of the cohort were Caucasian (n = 262), 5.7% Asian (n = 18), 3.8% Indigenous Canadian (n = 12), 2.2% Black (n = 7), 2.2% Middle Eastern (n = 7), and 3.8% of various other ethnicities (n = 12). PBC-40 scores slightly lower than those previously published in the literature were identified: out of a maximum score of 200, mean (SD) total PBC-40 scores were 86 (32) for Caucasian patients, 100 (32) for Asian patients, 127 (22) for Indigenous Canadian patients, 69 (37) for Black patients, and 86 (31) for Middle Eastern patients.

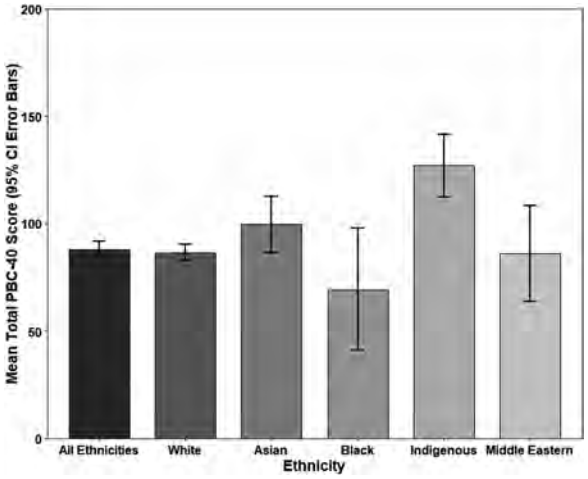

Figure: Mean Total PBC-40 Scores by Ethnicity

Indigenous Canadian ethnicity was associated with a mean total PBC-40 score that was 40 (95%CI 21–59) points higher than other Canadians ($p < 0.0001$). Indigenous Canadians were the only ethnicity whose mean total PBC-40 scores differed significantly from Caucasian patients ($p < 0.0001$). Investigation into which specific PBC-40 domains contributed to these worse scores revealed that Indigenous Canadians had significantly higher scores across all 5 domains of the PBC-40 compared to other Canadians (itch/symptom/

fatigue/cognitive/social-emotional: 3.1/4.8/11.7/8.2/12.3 additional points, p < 0.005 all domains). These differences in reported quality of life remained after adjusting for sex, age, centre, and duration of disease (itch domain p < 0.05, other domains p < 0.005).
Conclusion: When applying the PBC-40 in a multi-ethnic Canadian setting, quality of life burden among patients with PBC was substantially higher for Indigenous patients compared to other Canadians. Both the method of assessment, and approaches to improving quality of life in patients living with PBC, must be tailored to the population of patients served.

FRI180

Efficacy and tolerance of obeticholic acid in patients with primary biliary cholangitis and inadequate response to ursodeoxycholic acid in real life: interim analysis of the OCARELIFE study

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Background and Aims: Obeticholic acid (OCA), a selective farnesoid X receptor agonist, is currently the only approved second-line therapy for patients (pts) with primary biliary cholangitis (PBC) with inadequate response to ursodeoxycholic acid (UDCA). The objectives of the study were to evaluate the efficacy and the tolerability of OCA in the real-life setting in France.
Method: OCARELIFE is an observational, noninterventional, multi-site, ambispective study of pts with PBC who started OCA treatment in France between Oct 2016 and Dec 2017. Eligible pts had a diagnosis of PBC, an inadequate response to UDCA according to Paris II criteria, and had received at least 1 dose of OCA. The planned follow-up was 18 months (M). Clinical data and laboratory tests were collected at baseline (BL) and visits M1, M3, M6, M9, M12, and M18. Primary endpoint was the percentage of pts meeting Paris II criteria at M12.
Results: Interim analysis included 76 pts with consolidated data at BL. Most pts were female (87%) with a mean (standard deviation [SD]) age of 56 ± 11 years. Mean (SD) PBC disease duration was 10 ± 7 years. At BL, pruritus was present in 41% and considered severe in 7% of pts; mean (SD) total bilirubin and alkaline phosphatase (ALP) concentrations were 23 ± 33 µmol/L and 252 ± 201 IU/L, respectively. Liver biopsy was available in 84% of pts, and 41.5% of the pts had advanced fibrosis (METAVIR F3 or F4 or Scheuer stage 3 or 4) at BL. Transient elastography was available in 75% of pts: 50% had severe fibrosis defined as ≥9.6 kPa and 29% were >14.4 kPa. Seventy-two pts (95%) received UDCA at a median dose of 15.6 mg/kg, and 21 (28%) received fibrates. Efficacy was assessed in the 50 pts who temporally achieved M12 treatment period. Liver tests (mean) significantly improved after 12 months of treatment (Table). The percentage of pts with normal bilirubin increased from 61% at BL to 82% at M12. The primary endpoint of Paris II criteria was achieved by 40% (95% CI, 26.4–53.6) at M12. Liver stiffness did not change significantly. The main adverse events were fatigue (49%), pruritus (30%), and arthralgia (9%). Thirteen pts (17%) did not reach M12 due to pruritus. Three pts experienced serious adverse events, all of which were considered not related to therapy.
Conclusion: This real-life study including pts in severe condition demonstrated OCA efficacy and tolerability profile consistent with that observed in previous controlled trials.

FRI181

Lost in the system: identification of patients with undiagnosed primary biliary cholangitis

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Background and Aims: There is a renewed interest in Primary Biliary Cholangitis (PBC). The existence of inadequately detected patients, so called patients lost in the system (PLS), has been shown in other liver diseases as Hepatitis C. We aimed to investigate this issue in PBC.
Method: Database analysis (Immunology, Biochemistry, Reports, Appointments) of three reference Hospitals in Spain covering 1565000 healthcare population. PBC was diagnosed if AMA ≥ 1:80, chronically elevated alkaline phosphatase (ALP), and absence of other liver disease. Classification: 1) Baseline-detected PBC (diagnosis and treatment since the beginning); 2) Baseline PBC-PLS (absence of reports diagnosing PBC, medical follow-up and/or treatment with bile salts); 3) PBC development (previously normal ALP with elevation during follow-up); 4) PBC development-PLS (previously normal ALP subsequently elevated without detection or treatment). In patients with detected PBC, the delay time (DT) between first elevation of ALP and first request of AMA was also analyzed. Variables were expressed in n (%); median (IQR25-75); differences were assessed by T-test/U-Mann-Whitney (quantitative) or Chi-square (categorical); statistical significance was considered if p < 0.05.

Table

	n	Baseline	Month 12	Difference	95% CI		p value*
AST, IU/L	45	61.3	49	−12.3	−23.35	−1.32	0.0075
ALT, IU/L	45	66.2	46.6	−19.6	−34.35	−4.9	0.0002
GGT, IU/L	43	323.4	153.4	−170	−243.06	−96.62	< 0.0001
ALP, IU/L	42	250.8	188.1	−62.7	−122.84	−2.44	0.0042
Bilirubin, µmol/L	40	17	16.47	−0.53	−4.15	3.08	0.0790

*Wilcoxon signed-rank test.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; GGT, gamma-glutamyl transferase.

Figure: (abstract: FRI180)

Results: 1326 patients with AMA ≥ 1:80 (83.3% women, 56 years) between Jan/2010 – March/2019 were included: PBC 673 ([50.7%] 556 baseline-detected, 90 baseline-PLS, 18 development, 9 development-PLS), 653 with permanently normal ALP (49.3%). 99/673 (14.7%; CI95% 12–17.3) were identified as PLS. Of them, 26/99 have been contacted and retrieved for now (characteristics in Table 1). PBC has been confirmed and Ursodeoxycholic acid started in all. PBC development rate in patients with normal baseline ALP was 3.9% (27/680; median follow-up 2.96 ± 2.41 years). DT was 2.06 ± 3.89 years.

Table 1: Characteristics of retrieved patients

N = 26	(%)
Women	24 (92)
Other autoimmune disease	12 (46)
Pruritus	2 (7)
Fatigue	7 (26)
Elastography > 9.5 kPa	7/24 (29)
	Median (IQR)
Age (years)	70 (60–80)
Body Mass Index (kg/m^2)	27 (26–29.2)
ALP (UI/L)	185 (135–321)
GGT (UI/L)	101 (70–204)
Bilirubin (mg/dL)	0.6 (0.42–0.96)
Elastography (kPa)	7.1 (5.2–10)

Conclusion: Up to 14.7% patients (1 out of 7) with definitive diagnostic results of PBC remain undetected, preventing their monitoring and treatment. An effort to identify and retrieve these lost-in-the-system patients is necessary. The use of hospital databases is an appropriate tool.

Cirrhosis: ACLF and Critical illness

FRI182

Low growth hormone levels predict poor outcome of hepatitis B virus-related acute-on-chronic liver failure

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Background and Aims: Hepatitis B related acute-on-chronic liver failure remains a serious entity with high mortality. Growth hormone

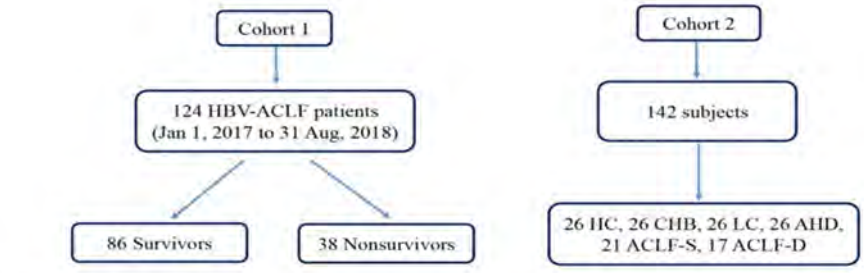

Figure 1 flow chart if enrolled cohorts.

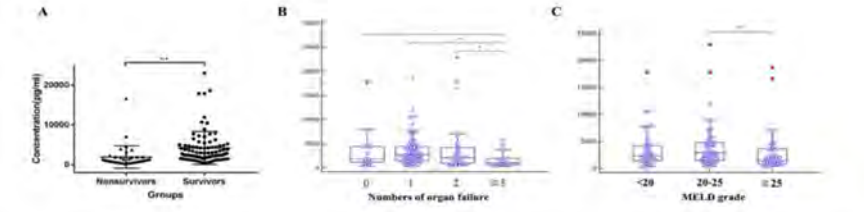

Figure 2 distribution of GH in HBV-ACLF cohort. (A) GH level was higher in survivors group than in nonsurvivors group. (B) Patients with 3 or more organs failure had lower GH levels than patients with 2, 1 or no organ failure. (C) Patients with MELD ≥ 25 had lower GH levels than patients with MELD between 20 and 25.*<0.05, **<0.01.

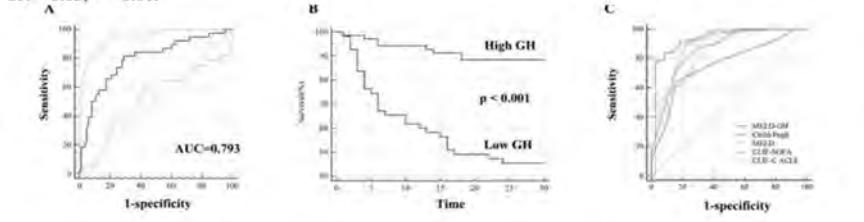

Figure 3 Performance of GH on predicting 30-day survival of HBV-ACLF patients. (A) the AUC of GH predicting the outcome was 0.793, and low GH(<2001ng/ml) group showed significantly worse 30-day outcome than high GH group. (C) MELD-GH score showed highest AUC than Child-Pugh, MELD, CLIF-SOFA and CLIF-C ACLF scores.

Figure: (abstract: FRI182)

(GH) is related to the liver metabolism and regeneration. The present study aimed to explore the changes and prognostic efficacy of GH on the outcome of HBV–ACLF.

Method: A prospective cohort of 124 patients and a cross-sectional cohort of 142 subjects were enrolled. History, complications, as well as image and laboratory measurements. Growth hormone (GH) and insulin-like growth factor-1(IGF-1) were detected by ELISA. 30-day survival was collected cirrhosis and the association between GH and the 30-day mortality of HBV-ACLF was analyzed.

Results: The mean age of the whole prospective cohort was 46.61 ± 12.71 years, and 19 (15.3%) patients were female. GH level was significantly higher in survivors than nonsurvivors of HBV-ACLF patients ($P < 0.001$), and it was correlated to white blood cell (WBC) count, albumin, blood urea nitrogen (BUN), etc. In the cross-sectional cohort, GH level was significantly higher in liver cirrhosis – acute decompensation group than liver cirrhosis group ($p < 0.001$). ACLF group didn't show any difference compared with liver cirrhosis- acute decompensation (LC-AD) group. The AUROC of GH for 30-day mortality was 0.793. Combining with MELD score, we built a new prognostic model, namely MELD-GH, which showed better predictive efficacy than Child-Pugh, MELD, CLIF-SOFA and CLIF-C ACLF scores.

Conclusion: Low GH predicted the poor outcome of HBV-ACLF patients. Combined with MELD, MELD-GH had better predictive accuracy when compared to Child-Pugh, MELD, CLIF-SOFA and CLIF-C ACLF scores. Pituitary function might play a role on ACLF, which need further research.

FRI183

Mesenchymal stem cells regulated DX5 – liver natural killer cells in rescuing acute-on-chronic liver failure murine

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Background and Aims: Acute-on-chronic liver failure (ACLF) is a severe, life-threatening syndrome with high mortality. Transplantation of Mesenchymal Stem Cells (MSCs) have been shown their efficacy in reducing mortality of ACLF patients in our clinical trials, but the mechanism is not clear, so unveiling the underlying mechanism of action will improve clinical regime of ACLF.

Method: Flow cytometry was applied to characterize natural killer cell (NK) from HBV-ACLF patients and ACLF mouse, and MSC developed in vitro.

An acute-on-chronic liver failure mouse model was established by injection of carbon tetrachloride (CCL4) intraperitoneally. Confocal microscopy was used to investigate cell-cell contact. Hematoxylin and eosin stained specimens and Bromodeoxyuridine incorporated liver tissues were investigated under microscopes. Western blot was used for hepatocellular death assay.

Results: Frequency of peripheral blood NK cells and frequency of NKG2A and KIR3DL1 on NK cells from HBV-ACLF patients were upregulated by MSCs infusion. Frequency of NKG2D, perforin and FasL were suppressed, which correlated with the recovery of liver function. MSCs infusion improved survival rate of ACLF mice efficiently (Log-rank $X2 = 3.88$, $P < 0.05$), coinciding with hepatitis remission, liver regeneration and NK frequency increase both in blood and liver. Meanwhile, MSCs were proved to promote the proliferation and GM-CSF secretion of NKP46+ DX5- liver NK cells specifically, which may be owing to their higher cell-cell (MSC-NKP46+ DX5- liver NK cells) adhesion.

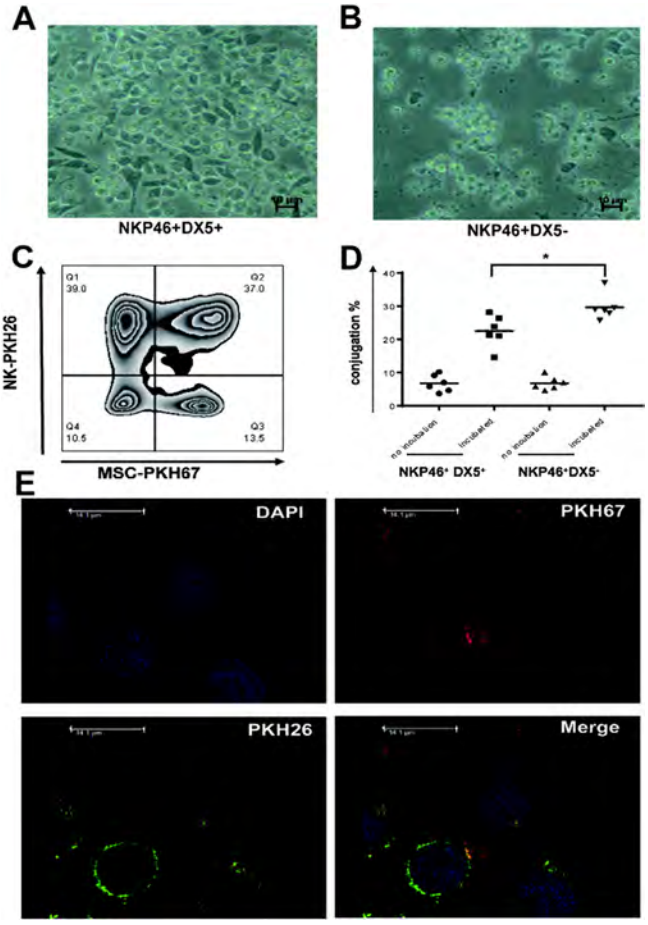

Figure: MSCs conjugated with NKP46+DX5- liver NK cells preferentially in vitro.

Conclusion: MSCs can rescue the ACLF patient and mouse by regulating NK cell. Promoting NKP46+ DX5- liver NK cells proliferation and secreting GM-CSF maybe the new machinery of MSCs' efficacy in ACLF.

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Selecting patients with decompensated cirrhosis and acute-on-chronic liver failure (ACLF) admitted to the intensive care unit for liver transplantation

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Background: ACLF is a clinical concept defined in patients with chronic liver disease who presented organ failure(s) secondary to an acute decompensated event. Liver transplantation (LTx) in this indication showed good results in selected patients. The aim of this prospective study was to evaluate the outcome and the factors associated with a favorable selection to LTx in this population.

Method: All consecutive patients admitted to the ICU with cirrhosis and ACLF, were recruited. Patient with age <18 years or with

fulminant hepatitis (including acute manifestation of Budd-Chiari, Wilson and auto-immune disease) were excluded.
Results: Between July 2017 and February 2019, 155 cirrhotic patients were admitted to ICU. Mean age was 55.6 ± 11.3 years (71.6% Male). Cirrhosis was due to alcohol in 78.1% of the patients. ACLF grading at admission was: 44.5% ACLF3 (n = 60), 21.3% ACLF2 (n = 33), 14.8% ACLF1 (n = 23), and 19.4% ACLF0 (n = 30).
Of the 155 patients, 46.5% (n = 72) were considered to be eligible for a transplant project and were assessed for LTx. The main reasons were alcohol abuse (66.3%, n = 55), death within 7 days after admission (32.5%, n = 27) and rapid improvement of the liver disease and discharged. Of the eligible patients 47.2% (n = 34) were transplanted with a mean time between admission to ICU and LTx of 57.9 ± 72.9 days. Twelve patients died on the waiting list (24% of the listed patients), mainly of septic shock and the remaining 5 patients are still awaiting. Among those who were assessed for LTx but not listed (n = 21), 76.2% died before the listing (n = 16) and 23.8% were not listed because of severe comorbidities (n = 5). The 28 and 90 days mortality rates were respectively 42.9% and 56.2%. The overall 3-month patient survival was respectively 97% and 26% in the transplant and non-transplant group ($p < 0.001$) for the entire cohort. Among eligible patients, factors associated with the absence of LTx, in the multivariate analyses, were mechanical ventilation (HR 8.95; 95% CI [2.75; 29.06], $p < 0.001$) and age over 60 years (HR 3.32; CI 95% [1.04; 10.63], $p < 0.001$).
Conclusion: Cirrhotic patients admitted to the ICU should be evaluated for eligibility to LTx. Merely half of the patients were eligible/assessed and 23% patients were transplanted. Among those eligible, patients over 60 years and under mechanical ventilation during early ICU stay would less likely to survive and be selected for LTx.

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Improving the survival rate of acute-on-chronic liver failure patients complicated with invasive pulmonary aspergillosis

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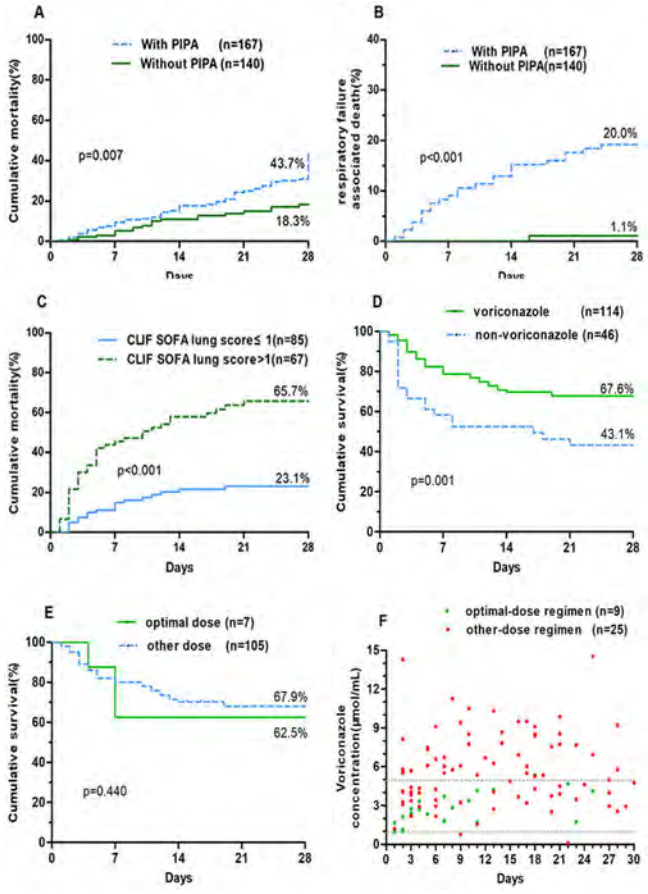
Background and Aims: Patients with critical liver diseases,especially acute-on-chronic liver failure (ACLF) are at high risk of developing infection. Fungal infection increases the mortality in ACLF patients. Data on invasive pulmonary aspergillosis (IPA) infection in ACLF patients is limited. This multicentre and retrospective study aimed to explore the prognosis and antifungal treatment in patients with IPA.
Method: This matched cohort study included ACLF patients from 15 tertiary hospitals in China between 2011 and 2018. In parallel, a control ACLF group in absence of IPA was enrolled at 1:1 ratio. Clinical features, laboratory data, micrological information, radiological findings, major causes of death,early prognostic indicators and antifungal options of patients with complicated IPA were recorded.
Results: We retrospectively analyzed 172 ACLF patients with IPA and 147 control patients. Respiratory failure was the main cause of death in patients with IPA. The 28-day mortality of IPA group was significantly higher than that of control group (43.7% vs 18.3%, $p < 0.001$) (Figure A). The 28-day mortality caused by respiratory failure in IPA group was significantly higher than in control group (20.0% vs 1.1%, $p < 0.001$) (Figure B). Furthermore, CLIF lung score >1 strongly predicted a short-term outcome of IPA patients (AuROC: 0.726). It was found that IPA patients with CLIF-SOFA lung score >1 had higher 28-day survival than those with lung score ≤ 1(65.7% vs 23.1%, $p < 0.001$) (Figure C). 164 of 172 (95.3%) patients received an antifungal therapy. Among multiple regimen, the voriconazole monotherapy was most common (42.1%, n = 69). Subsequently, the survival curves showed a significantly improved survival in those who received voriconazole-containing therapy (Figure D). There was no statistically significant difference in survival curves among an optimal voriconazole regimen (loading doses: 0.2 g twice daily; maintenance doses, 0.1 g once daily) (Figure E). Based on plasma voriconazole concentration measurement, an optimal voriconazole regimen was retrospectively validated, with optimal drug concentrations ranging from 1 to 5 μg/mL (Figure F).



Conclusion: IPA increases the mortality of ACLF patients and CLIF lung score predicts its outcome. An optimal voriconazole regimen might be safe and effective in ACLF patients with IPA.

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Soluble immune checkpoints are involved in the immunopathogenesis of ACLF

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Background and Aims: Acute on Chronic Liver Failure (ACLF) represents an immunological paradox. Patients exhibit a hyperinflammatory state at the clinical and molecular level that exists in parallel with a profound immunoparesis and increased susceptibility to bacterial infection. Immune checkpoints are key regulators of immune activation and their soluble forms have been shown in many contexts to modulate autoimmunity and responses to infection or malignancy. We therefore aim to explore their role in the initiation and propagation of the pathological immune response in ACLF.
Method: We quantified 17 soluble immune checkpoints by ELISA in the serum of 511 patients with decompensated cirrhosis included in the CANONIC Study; 334 with acute decompensation and 177 with ACLF at inclusion. Statistical analyses examined correlations with ACLF grade, clinical outcomes including survival and pro and anti-inflammatory cytokines.
Results: The soluble immune activatory checkpoints CD40 ($p < 0.001$), CD137 ($p = 0.009$) and CD27 ($p = 0.003$) increased significantly in the presence of ACLF and with increasing ACLF grade. The soluble immunosuppressive checkpoint BTLA (B and T-cell Lymphocyte-Associated) increased significantly in the presence of ACLF and with increasing ACLF grade ($p = 0.004$). Soluble CD80, which can be both inhibitory and stimulatory, also increased with ACLF grade ($p = 0.002$). Galectin 9 and Galectin 1, which have numerous immunomodulatory role showed similar increase. ($p < 0.0001$). Transplant-free survival at 28 days (CD40: $p < 0.001$, CD137: $p < 0.001$, CD80: $p = 0.035$, BTLA: $p = 0.035$, Galectin 9: $p = 0.027$, Galectin 1: $p = 0.027$) and 1 year (CD40: $p = 0.043$, CD137: $p < 0.001$, BTLA: $p < 0.001$, Galectin 9: $p < 0.001$, Galectin 1: $p < 0.001$) was also significantly associated with lower serum levels of certain immune checkpoints at presentation. Plotting the data as a heatmap demonstrates that levels of several checkpoint receptors increase in parallel in individual patients with increasing ACLF grades (Fig. 1).
Conclusion: We demonstrate increased levels of stimulatory and inhibitory soluble immune checkpoints with the presence of and increase in ACLF grade, and that higher levels of some of these factors associate with poorer clinical outcomes. We suggest that this activatory/inhibitory milieu is important in generating and maintaining the pathological hyperinflammatory hypoimmune state that is seen in patients with ACLF.

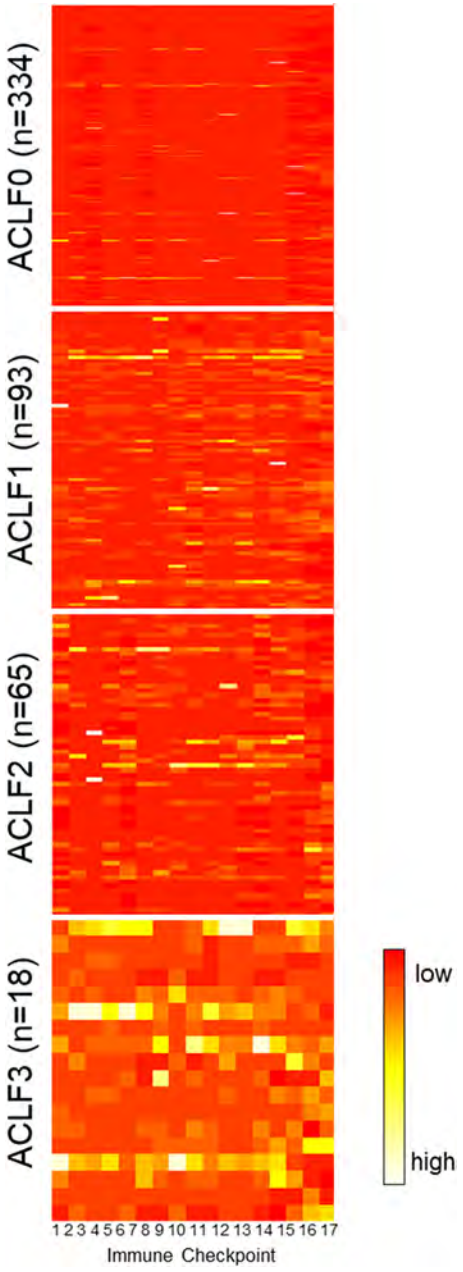

Figure: Levels of 17 soluble immune checkpoints by ACLF grade at presentation

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Prevalence, profile and predictors of invasive fungal infections in acute- on -chronic liver failure; analysis of Asia Pacific Association for Study of the Liver, Acute -on -Chronic Liver Failure Research Consortium (AARC) data base

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Background and Aims: Acute on chronic liver failure (ACLF) causes immune dysregulation and increased susceptibility to fungal infections. We studied the epidemiology, risk factors associated with invasive fungal infections (IFI) in ACLF. We correlated the timing of

occurrence, predictors of development, role of biomarkers in the diagnosis, antifungal prophylaxis with the outcome of IFI.
Method: The demographic, clinical and laboratory characteristics of ACLF patients, admitted to our tertiary care hepatobiliary centre, developing IFI were studied retrospectively based on the Asia Pacific association for the study of the liver (APASL) ACLF Research Consortium (AARC) data base. The diagnosis of IFI was based on revised definitions of invasive fungal disease from the European organization for research and treatment of cancer/Invasive fungal infections cooperative group and the national institute of allergy and infectious diseases mycoses study group (EORTC/MSG) consensus group. We also measured the biomarkers bronchoalveolar lavage (BAL) and serum Galactomannan index (GMI).
Results: Amongst 1670 patient with ACLF analysed. 320 (19.16%) who had appropriate host factors including recent history of neutropenia, prolonged use of corticosteroids or immunosuppressive therapy, and sufficient clinical evidence consistent with IFD but no mycological evidence were classified as possible IFI.60 (3.6%) who had host factors, clinical features, and mycological evidence consisting of direct test (cytology, direct microscopy, or culture) and indirect test, positive Galactomannan assay, were classified as probable IFI. Amongst the probable IFI group, the most common site of infection was urinary tract (n = 42/60, 70%) followed by respiratory (n = 12/60, 20%) and blood (n = 6/60, 10%). On univariate analysis, prior antibiotic use, high total leucocyte counts (TLC), acute renal failure, hemodialysis, diabetes mellitus, multi-organ failure, were predictors for development of IFI ($p < 0.05$). On multivariate analysis, TLC >14.3 × 10^3/ml^3, multi-organ failure, hemodialysis and prior antibiotics use predicted the development of IFI ($p < 0.05$). IFI occurrence was associated with significantly high 30 and 90 day mortality ($p < 0.001$). 68.4% patients with IFI in first 7 days of enrolment died as compared to 47.9% in control group ($p = 0.002$). BAL GMI (cut off ≥1) was positive in 38/60 (63.33%) and serum GMI was positive in 11/60, (18.33%). BAL GMI above 3.25 was better predictor of IFI (sensitivity 72.7%, specificity 51.5%).
Conclusion: Invasive fungal infections cause high mortality in ACLF patients. High TLC at admission, multi-organ failure, hemodialysis, prior antibiotics use and high BAL GMI predict the development of IFI.

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Differential hepatic mRNA and miRNA expression patterns in a novel mouse model of bacterial infection related to acute-on-chronic liver injury

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Background and Aims: Bacterial infection (BI) is a common acute trigger leading to acute-on-chronic liver failure in humans. Here we aim to establish a novel BI-ACLI model by LPS injection in a knock-out mouse with chronic hepatobiliary injury (*Abcb4*$^{-/-}$) to mimic disease conditions of ACLF.
Method: 15-weeks-old C57BL/6J (N = 16; wild-type, wt) and *Abcb4*$^{-/-}$ (N = 16; knock-out, ko) mice were treated with a single dose IP injection of either LPS (4 mg/kg) or saline (0.9% NaCl). qRT-PCR and stem-loop qRT-PCR were used to assess relative hepatic mRNA and miRNA expression. miRNAs 26a, 29a, 122, 143, 146, 192 m and Let7c, *Crp*, *Tnf-α*, *Rantes*, *Tgf-β*, *Tlr4*, *Mcp1* and interleukins (*IL*) 2, 6, 10, 17 and 22 were evaluated by $2^{-\Delta\Delta Ct}$ method.
Results: LPS resulted in a dramatic change in *Mcp1*, *IL-10*, *IL-6*, *Rantes* and *Tnf-α* expression with 200-, 63-, 45-, 38- and 31-fold increases in wt mice, and relatively moderate upregulation of *Crp* (4-fold), *IL-2* (5-fold), and *Tlr4* (6-fold). Corresponding effects were also observed in ko mice, whereby upregulation of *IL-6*, *IL-10*, *Tnf-α*, *Tlr4* and *Mcp1* was not significant. In line with the differential regulation of IL-22 and IL-17, where IL-6 alone is sufficient for IL-22 induction and high levels of IL-6 and Tgf-β are required for IL-17 upregulation, *Tgf-β and IL-17* did not differ among groups. More profound induction of *Rantes* (118-fold vs. 38-fold increase, $p = 0.037$), *IL-22* (75-fold vs. 5-fold, $p < 0.01$) and *Crp* (9-fold vs. 4-fold, $p = 0.026$) was present in ko mice as compared to wt. No *IL-22* was detected in NaCl-treated mice, whereas it was stimulated by LPS in both genotypes with a 7.3-fold higher upregulation ($p < 0.01$) in ko mice. Ko mice displayed higher basal expressions of miR-122 ($p = 0.029$), miR-192 ($p = 0.037$), and miR-143 ($p < 0.01$). Upregulation of miR-122 and miR-192 and repression of miR-143 and miR29a were evident upon LPS treatment without significant differences between genotypes. miR-26a, miR-146 and miR-Let7c, which were previously identified as markers for liver fibrosis and inflammation, were neither affected by *Abcb4* deficiency nor LPS challenge.
Conclusion: We propose a novel approach to model BI-ACLI in *Abcb4*$^{-/-}$ mice with differential expressions of hepatic cytokines, chemokines and miRNAs after LPS challenge. We speculate that *IL-2*, *IL-22* and *Rantes* could specifically trigger inflammatory cascades with harmful consequences on disease progression in chronic hepatobiliary diseases.
This study was supported by BMBF LiSyM (031L0051).

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The prevalence of multi-resistant bacterial infections in patients with decompensated cirrhosis admitted to the intensive care unit

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Background and Aims: Multiresistant bacterial infections (MRBI) are a significant health burden in patients with decompensated cirrhosis. We aimed to evaluate the prevalence and in-hospital mortality of MRBI in patients with decompensated cirrhosis admitted to the intensive care unit (ICU).
Method: Extensive infectious workup was performed at admission, and whenever worsening (further decompensation, new organ failure, acute kidney injury, or changes in infectious biomarkers) occurred. Child-Pugh, MELD, CLIF-C-ACLF, SOFA scores, ACLF grade, and in-hospital mortality were registered. MRBI were defined as bacterial infections with vancomycin-resistant enterococci (VRE), methicillin-resistant staphylococcus aureus (MRSA), extended-spectrum beta-lactamase (ESBL) and carbapenemase-producing organisms (CPO), including extensive drug-resistant (XDR) species.
Results: Seventy-six patients with decompensated cirrhosis (Child-Pugh, MELD, CLIF-C-ACLF, and SOFA scores were 12.3 ± 1.94, 27.8 ± 7.84, 11.6 ± 2.3, and 10.2 ± 3.31, respectively) were admitted to the ICU, mainly due to hepatic encephalopathy (39.5%). Fifty-one patients (67%) were infected, 19 (37%) had multiple infection sites, and 35 (68%) had sepsis. The respiratory origin was the most frequent (30%). There were 18 (25%) MRBI with the following etiologies: 4 VRE (22%), 4 ESBL (22%), and 10 CPO (55%). Thirty-nine patients had grade 3 ACLF

at admission. Among them, 28 (71%) were infected, of whom 10 (35%) had MRBI. Worsening occurred in 63 patients, the development of new organ failure (circulatory or respiratory) being the most frequent (39%). Among those who worsened 30 had a new or a second infection, of whom 16 patients (53%) had MRBI with 21 infection episodes (4 patients having more than one infection), as follows: 2 VRE, 1 MRSA, 2 ESBL, 12 CPO, and 4 XDR. Fifty-eight patients (76%) died during hospitalization, 41 (71%) of those being infected, of whom 18 where MRBI (44%). Sepsis-related multiorgan failure was the most frequent cause of death (44.8%). The median ICU stay was 9.8 ± 11.8 days. Median ICU stay, previous antibiotic therapy, and MELD score ≥20 at admission were associated with MRBI at worsening.

Conclusion: CPO was the most frequent etiology of MRBI in patients with decompensated cirrhosis admitted to the ICU. The development rate of a second infection with CPO increased with the length of ICU stay.

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Acute-on-chronic liver failure as defined by the European (EASL-CLIF) versus North American (NACSELD) diagnostic criteria in their prediction of short-term prognosis in patients with decompensated cirrhosis admitted into hospital

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Background: Both the European (EASL-CLIF) and the North American (NACSELD) ACLF definitions, each describing a different number of organ systems and using different parameters to define organ failures (OF), are predictive of prognosis in decompensated cirrhosis.

Aims: To compare the CLIF-C-OF score (the Sequential Organ Failure Assessment score modified for patients with chronic liver disease) vs. the NASCELD score in the prediction of prognosis in ACLF.

Method: 5 NACSELD centres provided prospective demographic and clinical data on patients with cirrhosis admitted non-electively. Patients were followed for the development of organ failure, hospital course, and survival. Baseline models were derived using a backward elimination multivariable logistic regression including all admission variables significant at $p < 0.10$. To determine the impact of NACSELD vs CLIF definitions of ACLF on (a) ICU transfer & (b) inpatient mortality, we first compared CLIF OF (range 0–6) to NACSELD OF (range 0–4), and then CLIF ACLF Grades (range 0–3) to NACSELD ACLF (Yes/No).

Results: 1031 patients were included, aged 57 ± 11 ys, 66% men with mostly alcoholic cirrhosis (47%). Admission reasons were infection (25%), HE (17%), GI bleed (16%) and renal dysfunction (12%). Admission Child-Pugh score was 9.6 ± 2.2 and MELD was 20 ± 8. More patients had renal failure (28% vs 9% $p < 0.001$) using CLIF vs NACSELD, but respiratory (3% vs 4%, $p = 0.28$), circulatory (4% vs 4%, $p = 1.0$) & brain failure (12% vs 12%, $p = 1.0$) were similar.

ICU transfer: Compared to baseline models, CLIF and NACSELD models were significantly better in the prediction for ICU transfer whether using # OF or ACLF grade and presence. NACSELD # OF had better prediction for ICU transfer compared to CLIF # OF. No significant differences were found comparing NACSELD vs CLIF on ACLF grade or presence analyses.

Table: Baseline models for prediction

ICU transfer		In-hospital mortality	
Alcohol Etiology Refractory Ascites Admission β-blockers use Rifaximin use Heart rate Hemoglobin WBC MELD score		Age Admission WBC MELD score	
vs. Baseline model			
CLIF #OF, p = 0.006	CLIF grade, p = 0.003	CLIF #OF, p = 0.35	CLIF grade, p = 0.27
NACSELD #OF, p = 0.0002	NACSELD (Y/N), p = 0.001	NACSELD #OF, p = 0.09	NACSELD (Y/N), p = 0.05
CLIF vs. NACSELD #OF, p = 0.04	Grade/presence, p = 0.92	#OF, p = 0.16	Grade/presence, p = 0.31

In-hospital mortality: Compared to baseline models, using OF analyses, there was trend towards better prediction by NACSELD but not by CLIF. With the ACLF grade/presence analysis, NACSELD added significantly to the baseline model while CLIF did not. No significant differences were found comparing NACSELD vs CLIF on ACLF grade/presence analyses.

Conclusion: The NACSELD # OF score, using admission parameters easily obtainable at the bedside without the need for an App, is equally, if not more effective than the EASL-CLIF score in the prediction of prognosis in inpatients with cirrhosis.

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Novel experimental animal models for acute decompensation and acute-on-chronic liver failure

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Background and Aims: The development of acute-on-chronic liver failure (ACLF) in patients with acute decompensation (AD) of chronic liver disease is associated with high short term mortality (up to 30–40%). Precipitating factors are known to induce AD and eventually lead to ACLF, which is defined by systemic inflammation, immune paralysis and organ failure. Still, the clinical picture of ACLF is largely variable, therefore different models are needed. The aim of this work was to characterise novel animal models for AD and ACLF to be used for drug development and testing.

Method: Cirrhosis was induced by bile duct ligation in rats (BDL; 28 days). They received either (i) a single intravenous injection of lipopolysaccharid (LPS) on day 21 (AD) or (ii) repeated injections on day 21 and 25 (ACLF). Portal and systemic hemodynamic changes were measured *in vivo*. Peripheral blood monocytes (PBMC), blood- as well as organ samples were collected at the end of the experiment. Markers of organ failure and systemic inflammation were characterized using cRNA Microarray, multiplex-based immuno-assay, western-blot and colorimetric assays.

Results: LPS significantly increased mortality in AD and ACLF rats (AD 15%; ACLF 50% at one week). The expression of inflammatory cytokines was induced in isolated PBMC from AD and ACLF rats and

in organs corresponding to the development of ACLF (liver, kidney, lung, brain, heart). Furthermore, circulating pro-inflammatory cytokines in peripheral blood were significantly increased, while anti-inflammatory cytokines were reduced. LPS injection induced hyperdynamic circulation in ACLF rats, demonstrated by increased portal pressure and cardiac output, as well as decreased systemic resistance. In line, intrahepatic and extrahepatic expression of endothelial cell function markers was dysregulated in ACLF rats. Bilirubin and creatinine levels were significantly increased in ACLF and renal perfusion was markedly reduced compared to untreated BDL rats.

Conclusion: The experimental models of LPS-induced AD and ACLF in BDL rats show the typical characteristics of human AD and ACLF (systemic inflammation, immune paralysis, hyperdynamic circulation, endothelial dysfunction and organ failure) and they could be suitable to investigate novel therapeutic strategies for patients in future.

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Artificial liver support system in hepatitis B virus-related acute-on-chronic liver failure patients

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Background and Aims: Hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) is difficult to treat and carries a high risk of short-term mortality. Unfortunately, as the result of no worldwide uniform diagnostic criteria for ACLF, it remains unclear that the effect of artificial liver support system (ALSS) on the prognosis of HBV-ACLF. This study aimed to compare the survival rate of HBV-ACLF patients treated with ALSS and standard medical treatment (SMT) alone, thereby gaining insight into the future improvement of HBV-ACLF prognosis.

Method: We selected 132 patients hospitalized to HBV-ACLF according with the criteria of Chinese Group on the study of Sever Hepatitis B-ACLF (COSSH-ACLF) (Gut 2018; 67:1–11) from 425 ACLF patients who were diagnosed to meet APASL criteria at least and followed up for 90 days. Among HBV-ACLF patients, 78 patients receiving ALSS, in which plasma exchange was the majority, and 54 patients receiving SMT alone were compared in terms of prognosis.

Results: The baseline characteristics of 78 patients treated with ALSS was comparable to that of 54 patients treated with SMT. The proportion of ACLF Grade 1, 2, 3 was 57.69%, 37.18%, 5.13% in ALSS group, 51.85%, 35.19, 12.96% in SMT group, respectively. There was difference in Child-Turcotte-Pugh score between ALSS group and SMT group, but no statistical difference in other baseline characteristics. The 28-day and 90-day mortality in the ALSS group and SMT group were 23.08% *vs* 48.15%, $P = 0.005$, 33.33% *vs* 57.41%, $P = 0.007$, respectively. Using Kaplan-Meier survival curve analysis, the survival time of ALSS at 28-day and 90-day were significantly higher than SMT group ($P < 0.05$). Multivariate Cox regression modeling showed that ALSS independently reduced the risk of 28-day death (HR 0.397, $P = 0.003$), besids total bilirubin (TBIL), international normalized ratio (INR) and Model for end-stage liver disease score (HR 1.382, 1.488, 1.054, $P < 0.05$). In addition, TBIL, INR, CLIF-C ACLF score and ALSS were independent factors affecting the survival time during 90 days. In HBV-ACLF Grade-1 group, compared with SMT alone, ALSS has a more significant effect on reducing the 28-day and 90-day mortality.

Conclusion: Based on the criteria of COSSH-ACLF, ALSS could obviously improve the short-term survival rate of ACLF patients than SMT alone, especially in ACLF Grade-1 of HBV-ACLF patients.

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Global hemostatic status in patients with acute-on-chronic liver failure and patients with sepsis without underlying liver disease

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Background and Aims: Patients with chronic liver disease (CLD) have substantial alterations in their hemostatic system. Remarkably, even in the sickest patients, such as those with acute-on-chronic liver failure (ACLF), the hemostatic system appears to remain in balance due to a concomitant decline of pro- and antihemostatic systems. It is, however, unknown whether the hemostatic status in ACLF is merely an exaggeration from the status in patients with compensated cirrhosis, or whether sepsis-associated hemostatic changes contribute.

Method: We performed extensive hemostatic profiling using functional tests and levels of markers of activation of hemostasis in 31 adult patients with ACLF, 20 with sepsis without underlying CLD, and 40 healthy controls (HC). Patients were longitudinally sampled over a 10 day period.

Results: Median MELD scores in ACLF patients on admission were 33 (IQR 26-40), and SOFA scores in sepsis patients were 6 (3–8). We found similarly elevated plasma levels of the platelet adhesive protein von Willebrand factor (VWF) and decreased levels of the VWF-regulating protease ADAMTS13 in both groups, compared to HC. In-vivo markers of activation of coagulation (TAT, D-dimer) were similarly elevated in both groups compared to HC, but ex-vivo

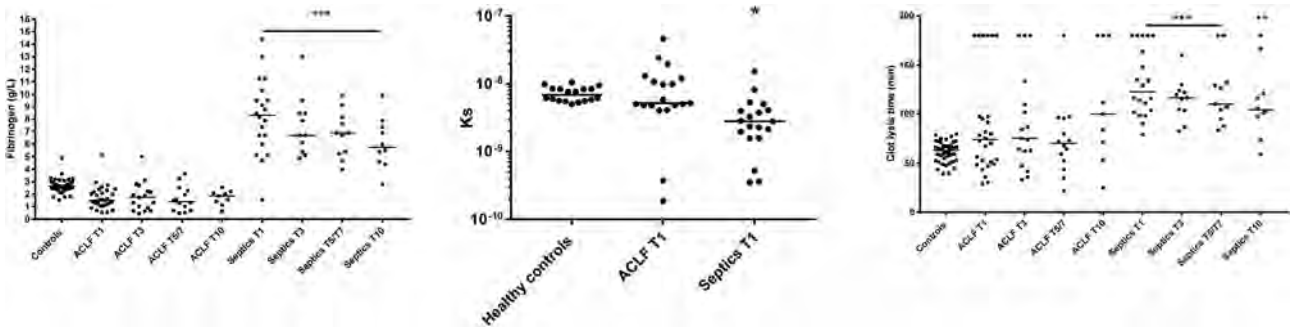

Figure: (abstract: FRI193): Fibrinogen levels, fibrin clot permeability, and plasma clot lysis time in plasma samples from healthy controls, patients with ACLF, and patients with sepsis without underlying liver disease sampled at various time points after admission.

thrombin generating capacity was similar between both patient groups and HC, despite a much more profound INR elevation in ACLF (INR of 2.4 [IQR 1.1–1.2] in ACLF vs 1.2 [1.1–1.2] in septics). Plasma fibrinogen levels were much higher in septics, which was accompanied by a decreased *ex-vivo* clot permeability and an increased in *ex-vivo* resistance to clot lysis (figure; * = significance vs controls). All hemostatic parameters were remarkably stable over the first 10 days after admission.

Conclusion: We have found hemostatic changes in ACLF to partially overlap with that of patients with sepsis, and evidence of preserved hemostatic capacity in both patient groups. The notable difference was a profound hyperfibrinogenemia with a thrombogenic clot structure and a profound *ex-vivo* resistance to fibrinolysis in patients with sepsis. A better understanding of the hemostatic status in both groups of acutely ill patients may facilitate a more rational approach to hemostatic management.

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Muscle quality as assessed by computed tomography-derived skeletal muscle density is associated with 28- day mortality in mechanically ventilated critically- ill patients with cirrhosis

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Background and Aims: Sarcopenia is known to adversly influence survival and transplant outcomes. Myosteatosis as assessed by computed tomography (CT) by analysing the skeletal muscle density (SMD), impacts the muscle quality. We investigated whether muscle quality is associated with 28 day mortality in critically ill cirrhotics.

Method: In this retrospective observational study of prospectively collected data of 117 mechanically ventilated patients admitted to the liver intensive care unit (LICU) between July 2018 to August 2019, 42 patients with a CT scan of the abdomen done 1 month prior or 4 days after ICU admissions were studied. The SMD was assessed for 80 mm^3 region of interest on the right and left psoas muscles and mean attenuation coefficient was expressed in HU. Skeletal muscle area (SMA), subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT) and intramuscular adipose tissue (IMAT) were analysed using the Slice-O-Matic software and expressed in cm^2. Multivariate stepwise (forward) logistic regression analysis was used to study the association between muscle quality and mortality.

Results: In 42 patients where complete data was available [M-36 (86%), age-48 ± 12.5 yrs; BMI-26.2 ± 4.9 Kg/m^2; diagnosis- cirrhosis 34(81%): ACLF 8(19%); etiology- Alcohol –22(52.4%): NASH-10 (23.8%): Viral-10(23.8%)], 28 day mortality was 71.4%. The survivors had more bleeders [4(33.3%) vs. 2(6.7%); p = 0.04)], lower prevalence of co-morbidities [3(25%) vs. 18 (60%)], lower CLIFSOFA score [8.9 ± 1.8 vs. 13.0 ± 4; p < 0.001], higher SMD [56.8 ± 5.1 vs. 48.6 ± 7.3; p = 0.001] and lower IMAT [3.8 ± 2.3 vs. 5.5 ± 2.1; p = 0.03] than non-survivors, though BMI, SMA, SAT and VAT were comparable. CLIFSOFA [OR (95% CI)]-1.55 (1.1–2.2);p = 0.019 and SMD 0.81(0.66–0.99);0.029 were the independent predictors of mortality also after adjustments for bleeding status and comorbidities. Mortality increased by 11% with every 1 unit increase in SMD. Cut-off of SMD <52.8HU would predict mortality (sensitivity = 75%, specificity = 76.7%, AUC = 80.8; p = 0.006).

Conclusion: Poor skeletal muscle quality as measured by SMD at ICU admissions is an independent predictor of 28 day mortality in mechanically ventilated patients with cirrhosis.

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Refining the renal failure criteria of the EASL-CLIF diagnostic model for defining acute- on- chronic liver failure (ACLF)

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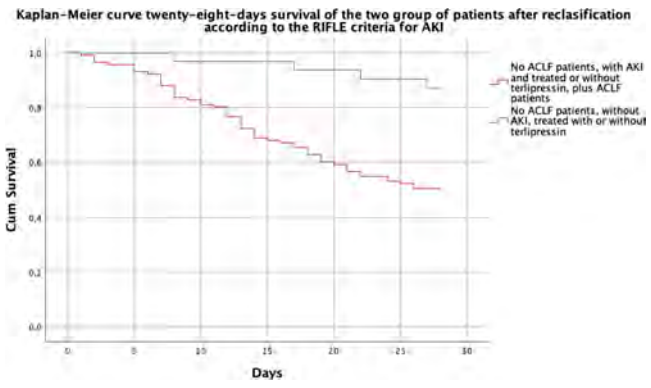
Background and Aims: Kidney function is estimated using serum creatinine (SCr). In cirrhosis, many factors affect values of SCr. The EASL-CLIF criteria for the diagnosis of ACLF uses static values of SCr to diagnose kidney failure. Recent changes in acute kidney injury (AKI) definitions would allow treatment of such patients earlier in their disease course, whilst application of existing SCr criteria (used to identify patients with a 28-day (28d) mortality of >15%) have been shown to have limitations by underestimating the presence of ACLF. The aims of this study were to evaluate whether the RIFLE classification, which has been extensively validated and stratifies AKI according to 3-classes of severity based on SCr or glomerular filtration rate (GFR), can be used instead.

Method: Retrospective analysis of prospectively collected data from 223 patients admitted to the ICU between 2005 and 2015, classified as having ACLF or no ACLF according to EASL CLIF criteria along with their 28-day mortality, was evaluated. Patients were then reclassified into different groups as having ACLF or not, with or without AKI using the RIFLE criteria and if they were treated or not with terlipressin. Mortality rate and survival analysis with Kaplan-Meier analysis were used.

Results: Patients with *no ACLF* (n = 69) had a high mortality rate (above the 15% threshold expected used for the EF-CLIF criteria) of 29%, which suggested that SCr criteria might under-diagnosed ACLF. Using the RIFLE criteria, patients with *no ACLF and no AKI* (n = 32) had 12.5% mortality at 28 d. Patients with *no ACLF but with AKI and not treated with terlipressin* (n = 11), and patients *with no ACLF but with AKI and treated with terlipressin* (n = 5) had a 28 d mortality of 63.6% and 20%, respectively. Reclassification using these new criteria to diagnose renal failure was applied and patients with high mortality risk (>15% at 28 d; those with *no ACLF and with AKI*), were allocated together with ACLF patients. When compared with *no ACLF and no AKI* patients, the 28 d survival was 20.6 days vs 26.8 days (p = 0.00) and 28 d mortality rate was 49.2% (odds ratio (OR) 6.77, p = 0.001; hazard ratio (HR) 1.65, p = 0.01) vs. 12.5% (OR 0.54, p = 0.04; HR 0.19, p = 0.001).



Conclusion: SCr underestimates kidney failure for the diagnosis of ACLF. Using the RIFLE criteria may more accurately identify 'kidney failure' within the EASL-CLIF criteria for ACLF. These data require further validation within larger patient cohorts.

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Regulation of IL-22 in a rat model for acute-on-chronic liver failure (ACLF)

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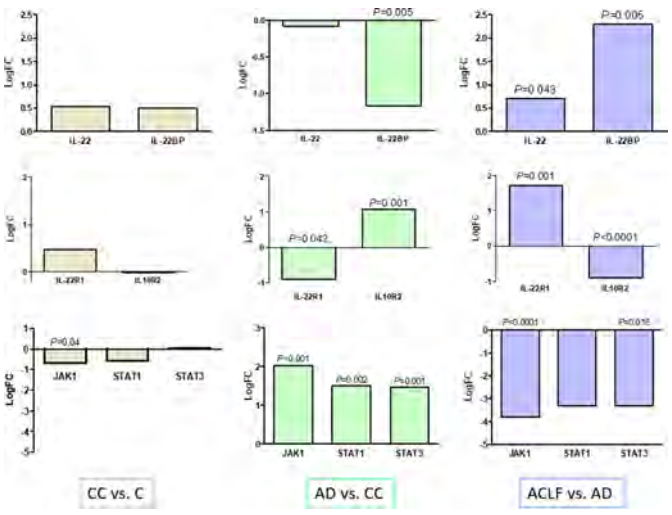
Background and Aims: Interleukin-22 (IL-22) may exert both hepatoprotective or hepatotoxic effects, as shown *in vivo* and *in vitro*. IL-22 binding protein (IL-22BP) is a soluble inhibitor of IL-22 signaling. Recently we were able to show that high levels of IL-22 and excessive secretion of IL-22BP are associated with ACLF and mortality of patients with cirrhosis. We investigated IL-22 signaling in rats with liver cirrhosis, acute decompensation (AD) and ACLF.
Method: Cirrhosis was induced in Sprague Dawley (SD) rats by bile-duct-ligation (BDL). Single administration of lipopolysaccharides (LPS) (6.25 µg i.v. on day 21; n = 5, group AD) lead to acute decompensation (AD) of liver disease with subsequent recovery of the animals. A second administration of LPS (6.25 µg i.v. day 21 and day 25, n = 4, group ACLF) induced ACLF with a mortality of 30%. Harvesting of organs and isolation of peripheral blood mononuclear cells (PBMCs) was performed on day 28 in all animals. The transcriptome was analyzed for changes in IL-22 signaling. As control groups served naïve SD rats (n = 5, group C) and cirrhotic rats with BDL (n = 5, group CC).
Results: IL-22 signaling was not altered in muscle, brain, duodenum, liver, heart, spleen, lung and kidney tissue. In PBMCs of rats with ACLF, IL-22 (ACLF vs. AD p = 0.043) and IL-22BP (ACLF vs. AD p = 0.005) were upregulated, whereas IL-22BP was downregulated in PBMCs of rats with AD (AD vs. CC p = 0.005). The IL-22R1 subunit of the IL-22 receptor complex was significantly upregulated in ACLF (ACLF vs. AD p = 0.001) while the IL-10R2 subunit of the IL-22 receptor was downregulated (ACLF vs. AD p = 0.0001). Comparison of AD vs. CC showed an opposite regulation of the receptor complex with a downregulation of IL-22R1 (AD vs. CC; p = 0.042) and upregulation of IL-10R2 (AD vs. CC; p = 0.001). Of note, GSK3B, a stabilizer of the IL-22R1/IL-10R2 complex was upregulated in AD (AD vs. CC; *P* = 0.022) but downregulated in ACLF (ACLF vs. AD p = 0.018). This resulted in a suppressed downstream signaling of IL-22 in ACLF (ACLF vs. AD; JAK1 p = 0.0001 and STAT3 p = 0.016) and an enhanced signaling in AD (AD vs. CC; JAK1 p = 0.005, STAT1 p = 0.002, STAT3 p = 0.001).



Conclusion: Our data suggest that IL-22 and IL-22 signaling are dysregulated in AD as well as ACLF and dependent on the severity of liver cirrhosis. Despite upregulation of IL-22 in rats with ACLF, downstream signaling is significantly decreased. A reason could be a reduced stability of the IL-22R1/IL-10R2 receptor complex.

FRI197

Thymosin alpha 1 for patients with hepatitis B virus-related acute-on-chronic liver falure: a randomized controlled trial

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Background and Aims: Mortality from hepatitis B virus (HBV)-related acute-on-chronic liver failure (ACLF) is high due to limited treatment options. The immunity of ACLF is like sepsis, and severe infection is the most important complication that affects the outcome of patients. As an immunoregulatory agent, we hypothesized that thymosin alpha 1 would improve the outcome of HBV-related ACLF.
Methods: From 2017 to 2019, 120 patients with HBV-related ACLF were enrolled in this open-label, nonblinded randomized controlled study (Clinical Trial ID: NCT 03082885). The control group (N = 58) was treated with standard medical therapy (SMT) only. The experiment group (N = 56) was injected 1.6 mg thymosin alpha 1 (THY) once a day for the first week and then twice a week for a total of 12 weeks subcutaneously.
Results: The 90-day cumulated survival rate of the THY group was 75.0% (95% confidence interval 63.3%–86.7%) versus 53.4% (95% confidence interval 40.2%–66.7%) for the SMT group (p = 0.03). There were no thymosin alpha 1 injection-related side effects. Compared with the control group, thymosin alpha 1 treatment markedly improved the international normalized ratio (INR) of patients. The incidences of new infection and hepatic encephalopathy in the THY group were much lower than that in the SMT group (25.0% vs 58.6%, p < 0.001; 8.9% vs 24.8%, p = 0.029, respectively). Mortality from severe infection in the SMT group was higher than in the THY group (24.1% vs 8.9%, p = 0.029).

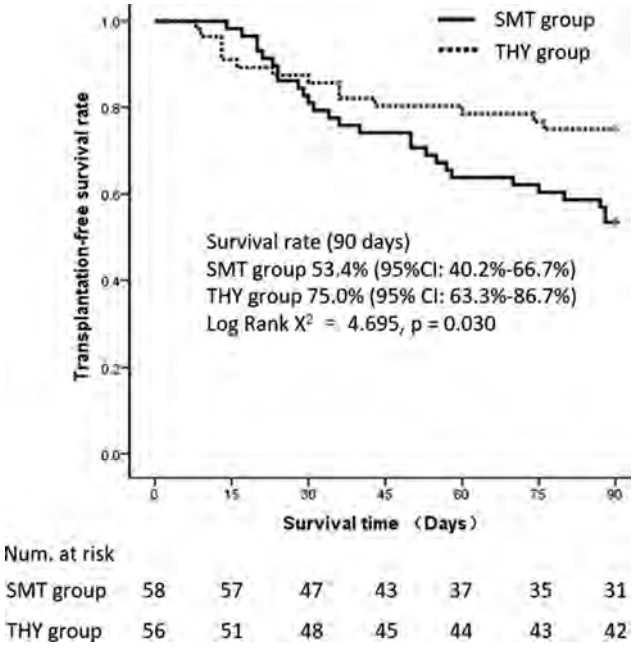

Figure: Kaplan-Meier survival curve of patients in SMT group and THY group

Conclusion: Thymosin alpha 1 is safe for patients with HBV-related ACLF and significantly improves the 90-day survival rate, due to decreasing the complications including severe infections and hepatic encephalopathy.

FRI198

Derivation and validation of prognostic nomogram for HBV-related acute-on-chronic liver failure

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Background and Aims: Liver transplantation is the only therapy that has been proven beneficial for hepatitis B virus(HBV)-related acute-on-chronic liver failure(ACLF). It is necessary to establish a simple and optimized scoring system to evaluate the patients' condition, so that liver transplantation can be performed on patients with greatest needed. This study aimed to establish an effective prognostic nomogram for HBV-related ACLF patients.
Method: The nomogram was based on a retrospective cohort (derivation cohort) of 1353 HBV-related ACLF patients who underwent comprehensive medical treatment at The Third Affiliated Hospital of Sun Yat-sen University from Jan 2010 to Jun 2016. The predictive accuracy and discriminative ability of the nomogram were determined by a concordance index (C-index) and calibration curve and were compared with the current scoring systems. The results were validated using bootstrap resampling and an independent retrospective cohort (validation cohort) on 669 HBV-related ACLF patients consecutively enrolled from July 2016 to March 2018 at the same institution. All statistical tests were two-sided. This study is registered at ClinicalTrials.gov (NCT03992898).
Results: Independent factors derived from multivariable analysis of the derivation cohort to predict 90 days' survival were age, aspartate aminotransferase(AST), total bilirubin(TBil), international normalized ratio (INR), creatinine, alpha fetal protein(AFP), hepatic encephalopathy(HE), infection, pre-existing chronic liver diseases(PreLD), and hepatitis B virus (HBV) DNA, which were all assembled into the nomogram. The calibration curve for the probability of 90 days' survival showed that the nomogram-based predictions were in good agreement with actual observations. The C-index of nomogram for predicting 90 days' survival were 0.786, which was statistically higher than the C-index values for Child-Turcotte-Pugh (CTP) (0.573, $P < 0.001$), Model for End-Stage Liver Disease (MELD) (0.664, $P < 0.001$), and MELD Na score (0.673, $P < 0.001$) in derivation cohort. The results were confirmed in the validation cohort. Besides, in validation cohort, the C-index of nomogram (0.787) was also higher than Chronic Liver Failure Consortium Organ Failure (CLIF-C OF) (0.727, $P < 0.001$), CLIF-C ACLF(0.746,$P = 0.005$) and Chinese Group on the Study of Severe Hepatitis B(COSSH) ACLF scores (0.762, $P = 0.012$).
Conclusion: The proposed nomogram resulted in more accurate prognostic prediction for HBV- related ACLF patients in South China.

FRI199

Efficacy evaluation of artificial liver support system (ALSS) in treatment of HBV-ACLF patients based on metabolomics

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Background and Aims: Hepatitis B Virus-related acute on chronic liver failure (HBV-ACLF) is characterized by rapid development, poor treatment effect and high short-term mortality. Liver transplantation is an effective treatment but is difficult to carry out large scales due to the shortage of liver source and high cost. Artificial liver support

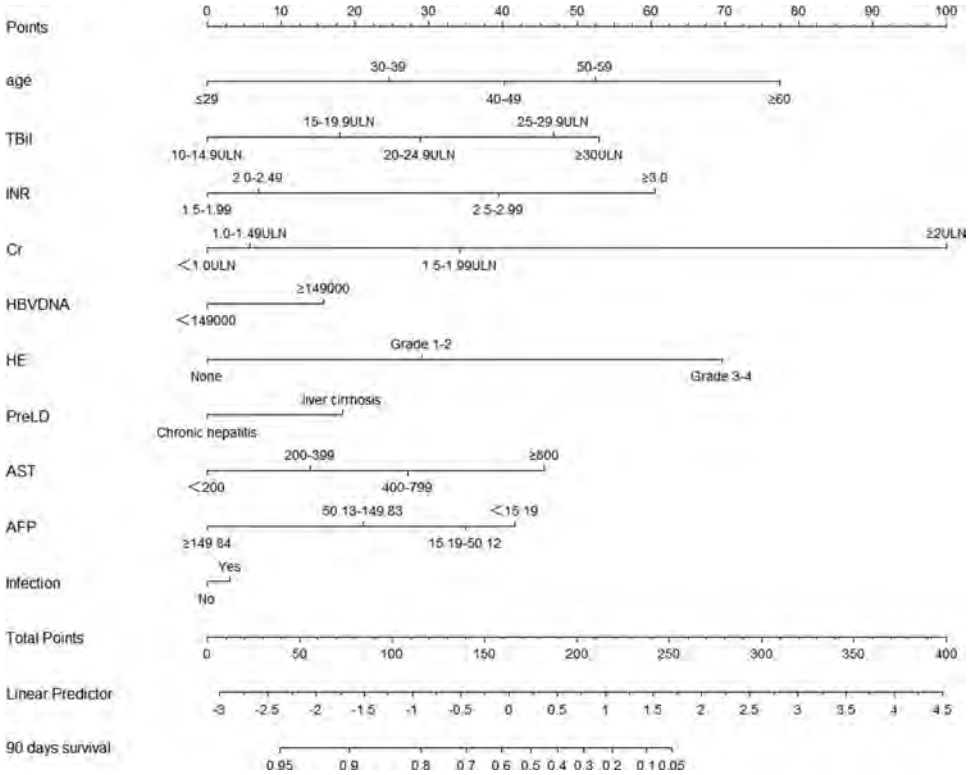

Figure: (abstract: FRI198): Nomogram for 90 days' survival in HBV-related ACLF patients.

system(ALSS) can effectively improve the survival rate of patients by temporarily replacing liver function. Liver is the main metabolic organ and the metabolic profiling could change during liver failure process. Analyzing the metabolites change is important to evaluate the efficacy of ALSS treatment of HBV-ACLF.
Method: Serum samples of HBV-ACLF patients were collected before and after ALSS treatment for three times. Multivariate analysis showed the metabolic trajectory changes before and after treatment. Based on serum samples acquired after the first treatment, the prognostic metabolites were screened out, and the trend difference between survival group and death group during the whole treatment process was investigated.
Results: Bilirubin and coagulation function improved significantly after ALSS treatment ($p < 0.001$). The OPLS-DA model of all samples revealed the metabolic trajectory changes before and after the ALSS treatment. Metabolite analysis showed a decrease in products of phenylalanine metabolism and an increase in glutamic acid, phenylpropionyl dipeptide and phospholipids after ALSS treatment. Phenylalanylphenylalanine and lysophosphatidylcholine were associated with disease severity and prognosis. Glutamyl substances were related to the prognosis of artificial liver treatment. Acylcarnitine substances and phenylalanyl-aspartate clearly differentiated between survival group and death group at the end of the treatment period.
Conclusion: ALSS therapy for HBV-ACLF can effectively remove excessive products of phenylalanine metabolism and supply phosphatidylcholine. Metabonomics provides new technique means to elucidate the pathological mechanism of HBV-ACLF.

FRI200
Mesenchymal stem cells regulate hepatocytes excessive autophagy and apoptosis through miR-125b/TRAF6 pathway in acute- on- chronic liver failure

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Background and Aims: Acute on chronic liver failure (ACLF) is a clinical syndrome with high mortality and lack of effective treatment. Previous clinical study confirm that mesenchymal stem cells (MSCs) can improve the prognosis of patients, but its mechanism remains elusive. Autophagy can be an adaptive response to provide energy and degrade the damaged intracellular components when the liver is subjected to varies injuries, however, in condition of ACLF, the cell necrosis is prolonged and more severe, the chronically activated autophagic process may lead to further cell death and worsen the disease. Recent lines of evidence indicate that the hepatoprotective effect of MSCs may through the regulation of autophagy, and the miR-125b, which is enriched in MSCs culture supernatant, play a major role to link autophagy and apoptosis, but whether and how it occurred during ACLF remains elusive.
Method: C57BL/6 mice were intravenously injected with carbon tetrachloride (CCL4) to generate a model of ACLF, and MSCs was transplanted through tail vein. The MSCs mediated autophagy and apoptosis in ACLF mouse and the role of miR-125b were examined in vivo and in vitro. The downstream target of miR-125b were identified in vitro and validated in vivo. Human liver tissues from ACLF patients and control individuals were obtained to evaluate the influence of miR-125b/TRAF6 on autophagy and apoptosis.
Results: The autophagic flux and hepatocytes apoptosis in ACLF mice were reduced by MSCs infusion, which were correlated with elevated miR-125b level. The anti-miR-125b oligonucleotide can make autophagy flux and hepatocyte death increase. TRAF6 was identified as a miR-125b target gene, knockdown of its expression in vitro can partially attenuated the effect of miR-125b inhibition via decreasing the inflammatory response in addition to reducing autophagy, which may be owing to repressing the activation of NF-κβ p65 and JNK. In human liver tissues, the expression of miR-125b was down-regulated in ACLF patients, both TRAF6 and autophagic flux were over-expressed in ACLF.
Conclusion: The hepatoprotective effect of MSCs may partially profit by miR-125b/TRAF6 mediating autophagy and apoptosis reduction, which may provide a new experimental basis for MSCs treating ACLF.

FRI202
Impact of acute-on-chronic liver failure and decompensated liver cirrhosis on psychosocial burden and quality of life of patients and their close relatives

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Background and Aims: Patients with liver cirrhosis often suffer from complications such as ascites, gastrointestinal bleeding, and infections, resulting in impaired quality of life. Frequently, the close relatives of patients also suffer from a lower quality of life in chronic diseases. In recent years, acute-to-chronic liver failure has been defined as a separate entity with high mortality. Often several organs are affected which makes intensive care therapy necessary. Little is known about the influence of acute-on-chronic-liver failure (ACLF) on the quality of life of patients and the psychosocial burden on close relatives. The purpose of this non-randomized prospective study is to investigate the influence of decompensated liver cirrhosis and the onset of ACLF of the patient's' quality of life and the psychosocial burden of close relatives.
Method: A total of 63 patients with acute decompensation of liver cirrhosis and hospital admission were enrolled in the study. To assess the quality of life of patients, the disease specific CLDQ questionnaire was assessed. In addition. quality of life and psychosocial burden of first-degree relatives was measured using the generic SF-36 questionnaire as well as the Zarit Burden Score.
Results: 21 of the 63 patients suffered from ACLF. Patients with ACLF showed a lower quality of life in terms of worries compared to patients with only decompensated liver cirrhosis and increased systemic symptoms. The univariate analysis confirmed the link between the existence of an ACLF and the concerns of patients. The organ failure score was significantly associated with overall CLDQ scores, especially with worries and systemic symptoms of patients. Interestingly the psychosocial burden and quality of life of close relative correlates with patient's quality of life and was influenced by the onset of an acute-on-chronic liver failure.
Conclusion: Patients with decompensated liver cirrhosis suffer from impaired quality of life. In particular, patients with ACLF have a significantly reduced quality of life. The extent of the psychosocial burden on close relative correlates with poor quality of life in patients with decompensated liver disease and is influenced by the existence of ACLF.

FRI203

Reversal of immune paralysis to immune homeostasis: effect of plasma exchange on monocyte merTK and HLA-DR expression in patients with acute- on- chronic liver failure

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Background and Aims: Acute on chronic liver failure (ACLF) is a clinical syndrome characterized by liver failure due to an acute hepatic insult on an underlying cirrhosis/chronic liver disease. MerTk negatively regulates immune cells and increases MerTk expression on monocytes in ACLF. It is associated with defective response to microbial challenge and decreased HLADR expression.
Plasma exchange (PE) by removing DAMPS, toxins and cytokines may readjust the immune system. We aimed to assess the impact of PE on HLADR and MerTK expression on monocytes in patients with ACLF.
Method: Whole blood samples from ACLF patients requiring plasma exchange (PE) (Gr.A; n = 12) and receiving standard medical therapy (SMT) (Gr.B; n = 10) were collected at baseline (Pre PE; Day 0), immediately Post PE (iPPE) and 24 hours Post PE (24hPPE) and Day 2 (D2) in SMT patients. Median fluorescent intensity of monocyte HLADR expression and frequency of MerTk expressing monocytes was assessed and compared with healthy controls (HC; n = 10) by flow cytometric analysis using FlowJo software. Biochemical parameters and clinical scores (MELD Na and AARC) were assessed in all patients.
Results: At baseline, Gr.A had significantly lower hematocrit (p = 0.04) and deranged PT/INR (p = 0.02) as compared to Gr.B. With PE in Gr.A, there was a significant drop in total bilirubin (p = 0.002), AST (p = 0.002), total protein & A/G ratio (p = 0.002) and PT/INR levels (p = 0.003) at iPPE. AARC and MELD Na scores also reduced significantly at iPPE (p = 0.004 and 0.008 respectively). There were no such differences in Gr.B on D0 and D2.
HLADR expression was significantly lower in ACLF patients in both groups compared to HC. However, monocyte HLADR expression increased significantly 24 hours after PE (p = 0.03) in Gr.A. However, in Gr.B, there was no difference in monocyte HLADR expression till D2. The frequency of MerTk expressing monocytes decreased significantly at iPPE in Gr.A (p = 0.01), as well as, on D2 in Gr.B (p = 0.02).
Conclusion: PE significantly improves liver function tests, indices of liver disease severity in ACLF patients. PE by abrogating the frequency of MerTk expressing monocytes and by restoring monocyte HLADR expression substantially restores immune homeostasis for a short interval. MerTk may act as a novel biomarker of monocyte function as well as a novel therapeutic target in sepsis.

FRI204

Different transcriptome characteristics of peripheral blood mononuclear cells are associated with survival outcome in hepatitis B-related acute-on-chronic liver failure

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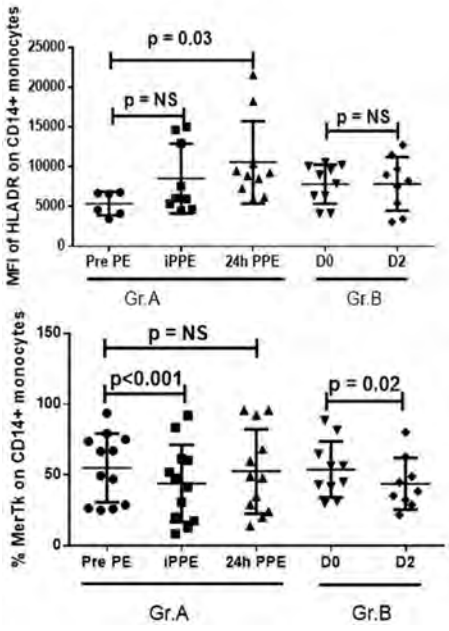
Background and Aims: Hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) is a specific syndrome involving the acute deterioration of liver function that could result in multisystem failure. The lack of knowledge of the exact molecular pathogenesis and broad-spectrum specific treatments contribute to the poor prognosis of HBV-ACLF. This study aims to find specific and sensitive biomarkers for predicting short-term mortality of HBV-ACLF using transcriptomics.
Method: It was a prospective cohort, in which all 16 HBV-ACLF patients met the Chinese Group on the Study of Severe Hepatitis B



	Plasma Exchange				Standard Medical Therapy		
	Pre PE	Post PE	24h Post PE	p value	Day 0	Day 2	p value
Total bilirubin (mg/dL)	29.4 (20-34)	21.7 (17-27)	22.4 (18-25)	0.002* 0.003**	22.1 (13-26)	22.7 (11-25)	NS
AST (IU/L)	99.5 (73-149)	85 (52-113)	78 (58.5-101.5)	0.002*	138 (105-166)	128 (120-159.5)	NS
Total Protein (mg/dL)	6.4 (6-7)	5.7 (5.5-6.5)	6.0 (5-7)	0.002*	6.7 (6.0-7)	6.7 (6-7)	NS
A/G ratio	0.7 (0.6-0.9)	1.0 (0.9-1.1)	0.8 (0.7-1.1)	0.002*	0.5 (0.3-0.6)	0.5 (0.4-0.6)	NS
PT (secs)	26.8 (23-31)	18.5 (17-20)	23.4 (19-28)	0.003* 0.01**	19.7 (16-27.5)	18.8 (18-33)	NS
INR	2.6 (2-3)	1.7 (1.6-1.9)	1.9 (1.8-2.4)	0.003* 0.01**	1.8 (1.5-2.6)	1.8 (1.6-2.9)	NS
AARC score	10 (8-11)	9 (7-10)	9.5 (7-11)	0.004*	8 (7-11.5)	7 (6-11)	NS
MELD Na	32 (29-35)	28.5 (24-32)	30 (26-33.5)	0.008* 0.01**	27.5 (24.5-35.5)	27 (24.7-37.5)	NS

Values represented as median (IQR), NS Not statistically significant
** p value between Pre PE and Post PE in Gr.A, ** p value between Pre PE and 24h Post PE in Gr.A*

Figure: (abstract: FRI203)

Table 1. Clinical characteristics of patients with HBV-ACLF at admission

Characteristics	Survival group (N=8)	Non-survival group (N=8)
Age (years)	42.8±10.5	57.8±11.8
Male (No.)	7(87.5)	6
BMI (kg/m²)	24.8±3.2	24.9±3.6
HBsAg (IU/ml)	1399.7±1513.3	36818.5±48072.6
HBV-DNA level(IU/ml)		
< 200	0	1
200-2X10⁴	2	0
2X10⁴-2X10⁵	5	2
≥2X10⁵	1	5
Laboratory data		
WBC (10⁹/L)	6.8±1.8	13±4.7
Hb (g/L)	125.8±18.4	135.8±22
PLT (10⁹/L)	115.8±50.4	115.5±18.4
ALB (g/L)	32.4+2.7	32.4±3.7
ALT (U/L)	316.4±383.7	808.6±875.7
AST (U/L)	148.8±111.3	480±.437.7
TB (μ mol/L)	360±86	333.2±91.6
Cr (μ mol/L)	59.7±17.3	119±116.2
Sodium (μ mol/L)	137.1±3.2	137.8±5.1
INR	2.0±0.2	2.6±0.3
AFP	977.8±2045	126.3±132.2
Severity score		
COSSH-ACLFs	5.8±0.4	7.2±0.8
CLIF-C ACLFs	37.0±4.5	54.7±5.5
MELD	21.3±2.7	28.4±6.7
MELD-Na	22.3±4.3	30.2±6.0

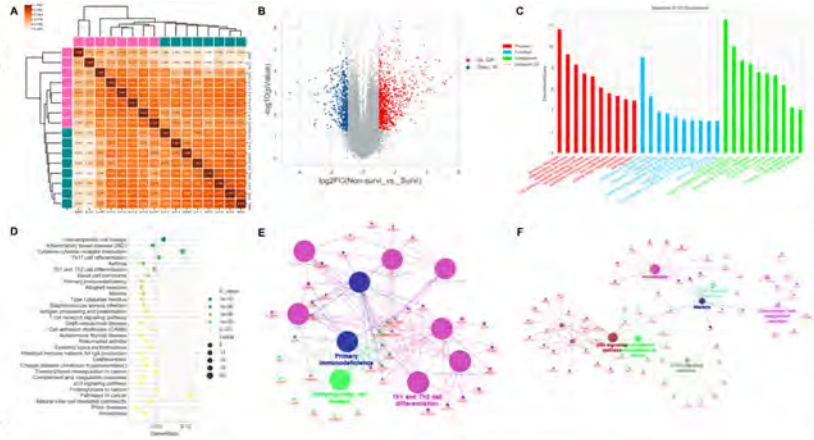


Figure 1. The gene expression profile characteristics of patients with HBV-ACLF. (A) The clustering results of the 16 patients. (B) Number of different probes detected between non-survival and survival groups. (C) The top 30 GO terms of all the differently expressed genes. (D) The top 10 KEGG pathways of all the differenlyt expressed genes. (E) & (F) The network of top 10 upregulated and downregulated KEGG pathways. Each node represents a KEGG pathway. Nodes are connected based on shared genes.

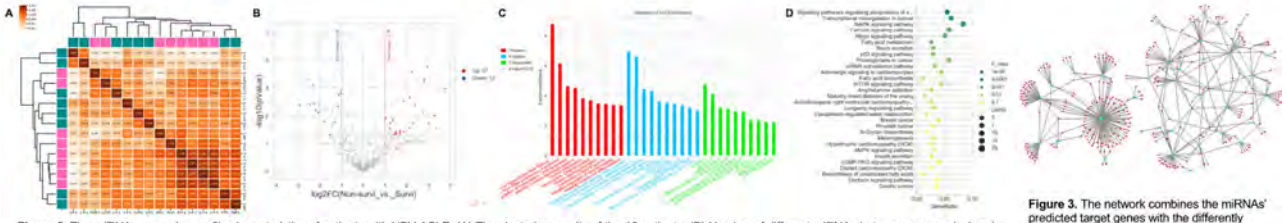


Figure 2. The miRNA expression profile characteristics of patients with HBV-ACLF. (A) The clustering results of the 16 patients. (B) Number of different miRNAs between non-survival and survival groups. (C) The top 30 GO terms of the predicted target genes. (D) The top 10 KEGG pathways of predicted target genes.

Figure 3. The network combines the miRNAs' predicted target genes with the differently expressed genes.

Figure: (abstract: FRI204)

(COSSH)-ACLF criteria. Clinical characteristics and peripheral blood mononuclear cells (PBMCs) were collected at admission for transcriptome and bioinformatics analysis.

Results: Analysis of gene expression profile showed that survival group was different from non-survival group obviously. The volcano Plot indicated that 1032 probes were significantly differentially expressed in non-survival group compared with survival group, of which 626 were upregulated and 406 were downregulated. Functional analysis of the differently expressed genes suggested immune response and inflammatory response played important parts in disease progression. The result of microRNA (miRNA) expression profile was similar. There were 39 miRNAs significantly differentially expressed in non-survival group compared with survival group.

Conclusion: Different transcriptome characteristics of PBMCs are associated with severity of liver damage, in which there are potential biomarkers for poor outcomes in HBV-ACLF cases.

FRI205

Granulocyte colony-stimulating factor in acute-on-chronic liver failure: systematic review and meta-analysis

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Background and Aims: Acute-on-chronic liver failure (ACLF) is characterized by an acute decompensation of cirrhosis, organ failure and high short-term mortality. A dysfunctional immune response underlies the pathogenesis of ACLF. The granulocyte colony-stimulating factor (G-CSF) mobilizes bone marrow-derived stem cells. It has been suggested that treatment with G-CSF may increase survival in patients with ACLF. The aim of the study is to assess the survival benefit associated with G-CSF administration compared to the standard of care in ACLF.

Methods: Systematic review and meta-analysis of randomized controlled trials. The primary outcome was long-term (60–90 days) survival. We searched PubMed from inception to October 2019. Manual searches of reference lists in relevant articles and conference proceedings from the European, North America and Asia associations for the study of the liver were also included (2009-present). GRADE system was used for quality and risk of bias analysis. Two independent investigators extracted the data and disagreements were solved by a third investigator.

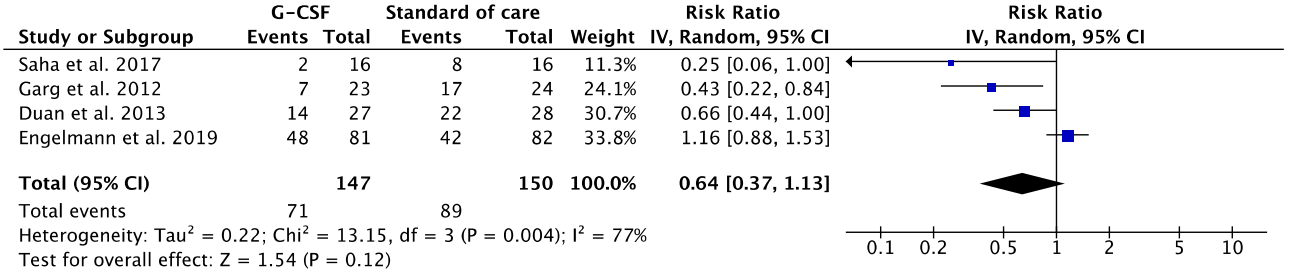

Figure: (abstract: FRI205)

Results: The initial search strategy identified 38 studies. Four randomized controlled trials were included for the quantitative analysis with a total of 297 patients (147 G-CSF and 150 standard of care). ACLF was defined by the Asian Pacific Association for the Study of the Liver criteria in all but one study (Engelmann et al 2019) which used the EASL-CLIF criteria. G-CSF regimens were 5 μg/kg/day for 6 consecutive days (Duan et al. and Saha et al.) and 12 doses of 5 μg/kg (Garg et al. and Engelmann et al.). Significant heterogeneity among studies was observed (I^2 = 77%, Chi^2 = 13.15, p = 0.004). Patients who received G-CSF did not show a significant overall survival benefit compared to the standard of care (random effects model, Risk Ratio = 0.64 [95% CI 0.37, 1.13]).
Conclusion: In a systematic review and meta-analysis, administration of G-CSF did not significantly improve transplant free survival in comparison with standard of care alone in patients with ACLF.

FRI206

Dysfunctional adaptive immunity in liver cirrhosis and acute-on-chronic liver failure is characterized by aberrant immune checkpoint expression and diminished cytokine secretion in T cells

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Background and Aims: Liver cirrhosis and acute-on-chronic liver failure (ACLF) patients suffer from high levels of systemic inflammation and parallel suppression of immunity. This was mostly demonstrated for innate immune cells where regulatory receptors and cytokine expression were upregulated. Yet, phenotypic changes in the adaptive immune cell compartment are not understood. We therefore aimed to characterize the development of T cells regarding their co-stimulatory and inhibitory marker expression as well as cytokine production during the progression of liver cirrhosis to ACLF
Method: Patients with compensated/stable decompensated liver cirrhosis, acute decompensation of liver cirrhosis, or ACLF were recruited from a prospective cohort study. Peripheral blood mononuclear cells (PBMCs) underwent flow cytometric immunophenotyping for 23 co-stimulatory and inhibitory cell surface markers. In addition, PBMCs were treated with PMA/Ionomycin and stained intracellular for cytokine production, i.e. TNFalpha and IFNgamma.
Results: Previous results of our group showed higher frequencies of detectable TT virus in patients with compensated/stable decompensated liver cirrhosis compared to healthy controls suggesting immunosupression as an early phenomenon in liver cirrhosis. On a phenotypic level, CD8+ as well as CD4+ T cells demonstrated parallel upregulation of numerous co-stimulatory (e.g. CD40L, OX40, CD69, GITR, TIM-1) and inhibitory immune checkpoints (e.g. PDPN, PROCR, 2B4, TIGIT), which again preceded the development of ACLF. Whereas all T cell types – CD8+, CD4+ and regulatory T cells (Tregs, CD4+ CD25dim CD127-) – displayed higher frequencies of the death receptor CD95 and the inhibitory marker PDPN, many changes occurred prominently within one subgroup, such as an upregulation of KLRG1 on CD8+ T cells and CTLA-4 on Tregs. On a functional basis, the capacity of CD4+ and CD8+ T cells to produce pro-inflammatory cytokines upon stimulation was strongly diminished in patients with acute decompensation of liver cirrhosis and ACLF.
Conclusion: Occurrence of dysfunctional T cell responses is an early event in the pathogenesis of liver cirrhosis and precedes ACLF. As a mechanism, abnormal expression of co-stimulatory and inhibitory markers provides an explanatory link towards immunosuppression and higher death cell rates. This might contribute to the development of ACLF by elevating the risk of infections in patients with liver cirrhosis.

FRI207

Functional activin-HNF4A-coagulation axis in liver progenitor cells determines MELD score and outcome of acute-on-chronic liver failure

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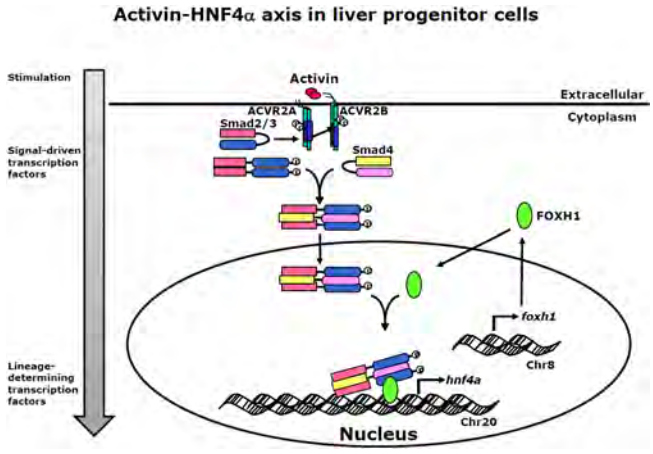
Background and Aims: Given the shortage of donors, only patients with MELD score ≥15 are on the waiting list for liver transplantation (LTx). Impressively, a lot of patients e.g. those with acute-on-chronic liver failure (ACLF) display successful hepatic regeneration in the explanted livers. This raises a controversial issue whether these patients should obtain donor livers. Liver progenitor cells (LPCs) are major cell source running hepatic function when a liver suffers from massive hepatic necrosis, a histological feature of ACLF. This study shows that LPCs in irreversible ACLF lose intact Activin-FOXH1-HNF4α regulatory axis, and thus cannot provide sufficient coagulation function, which results in high MELD scores and poor prognosis.
Method: Twenty-five ACLF patients (17 received LTx and 8 recovered) were enrolled. Clinical, blood biochemical and histological parameters were analyzed. The molecular mechanisms of how Activin-FOXH1-HNF4α axis exerted function were investigated in rodent LPCs.



Results: In vitro study showed that LPCs produce key hepatocyte functional genes/proteins, including coagulation factors and albumin. Expression of these genes was controlled by a lineage determination transcription factor HNF4α. Knockdown of HNF4α remarkably reduced expression of coagulation factor V (f5) and albumin. ChIP analysis confirmed the binding of HNF4α on the promoter of f5 and albumin genes. Further analyses showed that disruption of Activin specific receptor ALK4, downstream substrates (SMAD2, SMAD3 and SMAD4) and transcription factor FOXH1 significantly decreased HNF4α expression. Activin induced HNF4α expression. Co-IP analysis showed that Activin-induced p-SMAD2

formed a complex with SMAD4 and FOXH1. In most irreversible ACLF patients, immune positivity of p-SMAD2, FOXH1 and HNF4α was undetectable by immunohistochemistry. However, 8 recovered ACLF patients demonstrated robust expression of HNF4α in nuclei of LPCs and remaining hepatocytes. There was closed association between high levels of HNF4α expression, low INR and high MELD scores in ACLF.

Conclusion: These results revealed that Activin provides a key signal stimulating HNF4α to govern expression of coagulation factors in ACLF. Impairment of Activin-HNF4α axis causes high MELD scores. Even if these patients complete LPC-mediated regeneration, LPC-derived hepatocytes still are not capable of running intact hepatic function. LTx is the only option to rescue these patients.

FRI208

Serum cholinesterase, an underestimated marker in the prediction of acute-on-chronic liver failure, organ failure and LTx-free survival in patients with liver cirrhosis?

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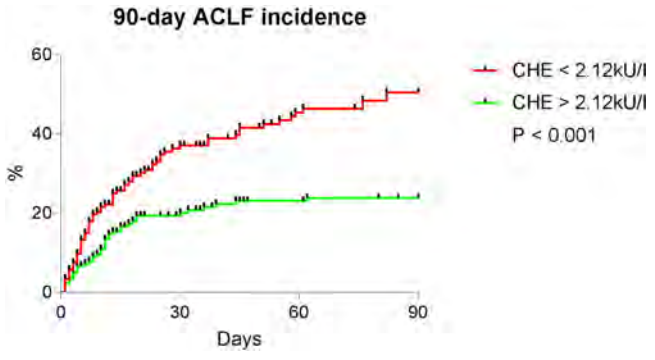
Background and Aims: Acute-on-chronic liver failure (ACLF) is associated with a high short-term mortality and defined as the combination of acute decompensation and organ failure (OF) in patients with liver cirrhosis. In clinical practice, it is often challenging to determine which patients will develop OF and ACLF. Serum cholinesterase (CHE) is closely associated with the synthetic function of the liver. However, its prognostic value in patients with liver cirrhosis, in particular in terms of ACLF development, remains unclear. Thus, we aimed to investigate the prognostic value of CHE in these patients.

Method: Overall, 521 hospitalized patients between 2012 and 2018 with liver cirrhosis were considered for this study. Patients with ACLF at admission were excluded, leaving 353 patients for further analyses. Study endpoints were 90-day (90d) incidence of ACLF, 90d incidence of distinctive OF (i.e. liver, kidney, cerebral, circulatory, respiratory, coagulation) and 90d liver transplant (LTx) free survival. ROC-analysis was used to determine optimal CHE cut-off values associated with ACLF. For survival analysis uni- and multivariate Cox-regression were conducted, adjusting for MELD, leukocyte count, age and serum-sodium.



Results: Overall, 132 (38%) patients were female, mean age was 57 years and the mean MELD score was 15.8. The optimal cut-off for CHE to determine 90d ACLF development was 2.12 kU/l ($p < 0.001$). CHE <2.12 kU/l was associated with a higher 90d-incidence of ACLF (HR:2.30; $p < 0.001$) (Figure 1). In the multivariate model only CHE <2.12 kU/l, age and MELD score were independently associated with 90d-ACLF development (HR:2.02; $p = 0.001$, HR:1.02; $p = 0.03$ and HR: 1.09; $p < 0.001$, respectively). Regarding specific OF, CHE <2.12 kU/l was independently associated with kidney failure, cerebral failure, circulatory failure and coagulation failure (HR:2.04; $p = 0.002$, HR:4.15; $p = 0.01$: HR:1.97; $p = 0.002$; HR:3.49; $p = 0.001$). Of note, liver failure and respiratory failure were not linked to CHE values <2.12 kU/l (HR:1.38; $p = 0.26$, HR:1.77; $p = 0.19$). However, CHE <2.21 kU/l was associated with lower LTx-free survival (HR:3.20; $p < 0.001$). Interestingly, in patients with MELD scores <15 only CHE <2.12 kU/l and leukocytes but not the MELD score were independently associated with 90d-survival (HR: 5.76; $p = 0.01$ and HR:1.11; $p = 0.04$).

Conclusion: In patients with liver cirrhosis CHE values may help to identify those with a high risk for ACLF, organ failure and mortality.

FRI210

Single- centre experience of implementing a hepatology outreach service to improve patient care for emergency admissions of acutely decompensated cirrhosis

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Background and Aims: Decompensated cirrhosis is a medical emergency associated with high in-patient mortality. Despite the introduction of the BASL/BSG care bundle in the UK, emergency admissions due to decompensated cirrhosis are often sub-optimally managed in non-specialist areas. In this study we reviewed patient care before and after introduction of a consultant- led hepatology outreach service to acute clinical areas.

Method: After our outreach service had been active for three months, we reviewed patient records for all emergency admissions due to decompensated cirrhosis and compared these to the same three-month period, three years before the induction of the outreach service. We recorded whether elements of the BASL/BSG care bundle were completed within 24 hours as well as the length of stay (LoS), intensive care unit (ICU) admissions, mortality and 90-day outcomes following discharge.

Chi-squared analysis was performed to identify any statistically significant results.

Results: 21 cases met the inclusion criteria and were included in the pre-intervention group and 28 cases in the post-intervention group. An improvement in compliance with the BASL/BSG bundle was noted within 24 hours of admission, with patients being more likely to receive blood cultures, abdominal ultrasound scans and paracentesis ($p < 0.05$). Once admitted, the proportion of patients receiving specialist reviews within 24 hours increased from 50% to 68% ($p < 0.05$). Post intervention a reduction in intensive care unit admissions and re-admissions within 90 days was noted. However, length of stay increased from 11 to 16 days. Despite improvements in care, mortality rates remained high (Figure 1).

Conclusion: Decompensated cirrhosis is an acutely life-threatening condition. Our results show that support of the acute medical team through early specialty review improves patient care during their initial admission and has resulted in reduced re-admissions.

These data, demonstrating improved patient care and outcomes, have resulted in adoption of a permanent in-reach service in our hospital, and a prospective analysis of the service will inform future service development.

	2016	2019	p-value
Bone profile	29% (6/21)	43% (12/28)	0.08
Blood cultures	19% (4/21)	39% (11/28)	0.03*
Abdominal ultrasound	19% (4/21)	61% (17/28)	<0.01*
Ascitic tap	35% (7/20)	56% (9/16)	0.02*
Alcohol intake documentation	71% (15/21)	74% (17/23)	0.63
IV Pabrinex administered (if alcohol excess)	44% (8/18)	55% (11/20)	0.34
Appropriate treatment with lactulose (if encephalopathic)	67% (2/3)	100% (8/8)	0.03*
Hepatology review within 24 hours	50% (10/20)	68% (19/28)	0.04*
90-day mortality rate	19% (4/21)	29% (8/28)	0.12
ICU admission	19% (4/21)	13% (3/24)	0.30
90-day re-admission rate	37% (7/19)	25% (6/24)	0.14
Length of admission (days)	11	16	

Figure 1: (abstract: FRI210): Patient outcome pre vs post introduction of hepatology outreach service.

FRI211

Using bilirubin to define hepatotropic insult in patients with chronic liver disease and acute exacerbation: a prospective multicenter cohort study

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Background and Aims: Serum total bilirubin (TB) is the critical indicator to judge whether the patients with acute exacerbated chronic liver disease (CLD) are suffering from a hepatotropic insult and benefiting from expedited liver-specific treatments. However, definition is of hepatotropic insult blurry. We aim to explore the evidence-based TB cutoff value to define it.

Method: Two prospective, multicenter cohort studies were conducted in china. We consecutive enrolled 2600 (from Jan.2015 to Dec.2016) and 1370 (Sep.2018 to Jan.2019) patients with CLD hospitalized for acute decompensation (AD) or acute liver injury. Patients' characteristics at admission and their 90-day outcome were collected. TB value (mg/dL) was normalized by natural logarithm. We used local weighted scatter smoothing (LOWESS) model to visualized the relationship between TB and 90-day LT-free mortality (LTF-M). Rational equations were used to fit and calibrate the curves' functions. Second derivatives were used to describe the mortality's acceleration and calculated the cutoff of TB.

Results: Among all 3970 patients enrolled, 70.8% were HBV related, 71.2% were cirrhotic, and 81.1% were with AD. We found patients' 90-day LTF-M acceleratingly climbs as the TB increases. Therefore, we made a hypothesis that value of TB at the maximum acceleration point is the cutoff value of hepatotropic insult, then via a rational equation, we calculated it [ln (TB) = 2.49, TB = 12 mg/dL, Figure 1A, B]. 1168 patients (TB ≥12 mg/dL) and 2792 patients (TB<12 mg/dL) were compared. The group of patients with higher TB [20.7 (15.9 – 27.4) vs

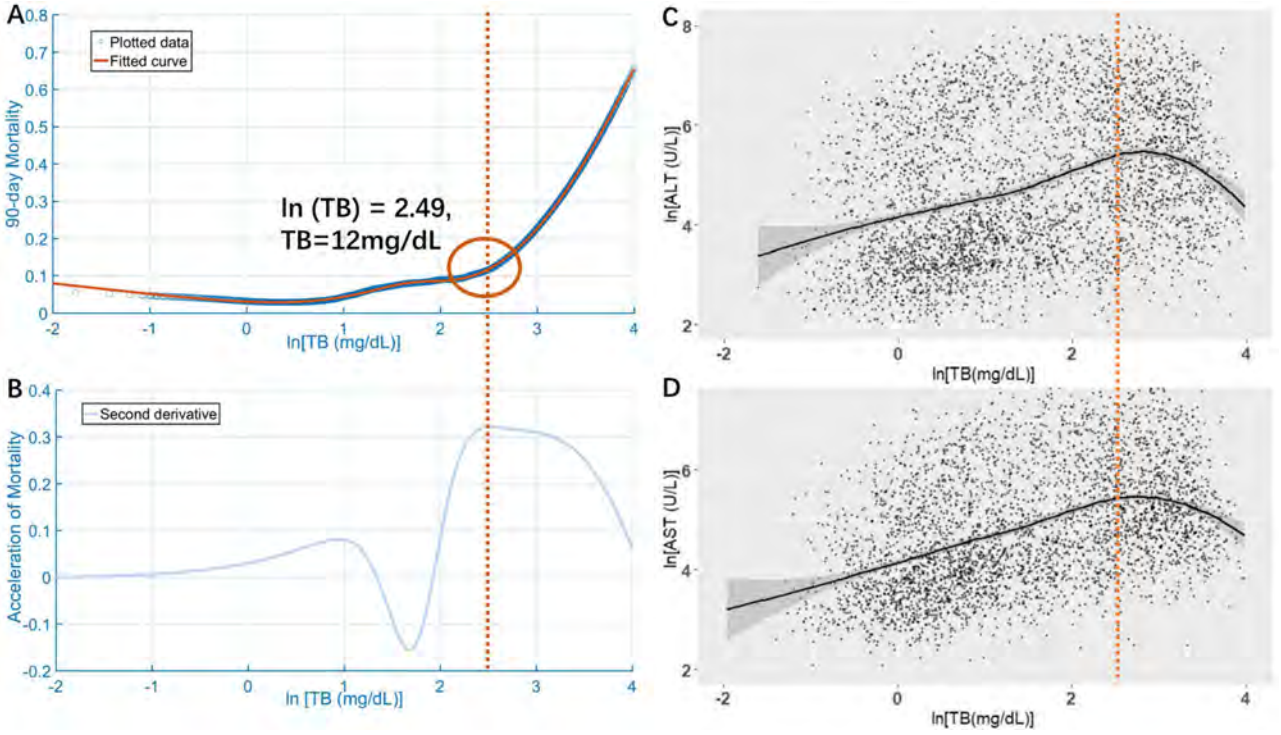

Figure: (abstract: FRI211): **Legend A** Relationship between TB and 90-day LT-free mortality; **B** the Second derivatives curve shows the mortality's maximum acceleration; **C, D** Relationship between TB and ALT; **D** Relationship between TB and AST.

2.3 (1.2 – 4.9), p < 0.001] show much higher 90-day LTF-M (31.2% vs 6.0%, p < 0.001), transaminase, INR and MELD score [25.0 (22.0 – 29.0) vs 12.0 (9.0 – 17.0), p < 0.001], but only slightly elevated creatinine [0.8 (0.6–1.0) vs 0.8 (0.6–0.9), p < 0.001] and lower rate of gastrointestinal bleeding (3.2% vs 19.3%, p < 0.001). Additionally, we found that when TB exceeds 12 mg/dL, its correlation with transaminase is reversed (Figure 1C, D).

Conclusion: First time hepatotropic insult is clearly defined as TB ≥ 12 mg/dl, which was obtained from large scale cohort data and mathematical model instead of expert consensus in HBV high-endemic region.

FRI212

Clinical features and natural history of acute-on-chronic liver failure precipitated by any indeterminate factor: single-center observational study

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Background and Aims: Acute decompensation (AD), along with subsequent acute-on-chronic liver failure (ACLF) of patients with liver cirrhosis (LC) may be fatal and impairs quality of life. How a precipitating factor (PF) of ACLF influences prognosis is still largely unknown. Studies from different regions of the world reported that about 10 to 40% of ADs/ ACLFs were precipitated by any acute insult that was not identifiable. In the current study, we aimed to clarify the clinical features and the natural history of AD/ACLF with any indeterminate PF.

Method: In this single liver transplant center observational study approved by local institutional IRB (no. 20170202), we retrospectively recruited 1532 consecutive admissions to our liver unit from Jan 2012 to Apr 2019. After exclusion of admissions for planned procedures, 220 cases (58% male; aged 62.8 ± 15 years) with AD were extracted for analysis. PFs of each AD were reviewed retrospectively. Transplant-free survival (TFS) within 180 days and clinical parameters were compared by PFs.

Results: The median observation period 380 days. Twenty cases (9%) underwent liver transplantation (LT), 52 (23%) suffered from liver-related death, 114 (51%) survived without LT, and the remaining deceased due to non-hepatic cause or lost follow-up (17%); 29% met the EASL CLIF-C criteria of ACLF grade 1–3, and 51% met the APASL criteria of ACLF. PFs included bacterial infection (INF-AD; 23%), GI bleeding (15%), active alcoholism (13%), superimposed/ exacerbated hepatic viral infection (3%), others (trauma or procedure-related, 9%), and indeterminate (IND-AD; 38%). By Kaplan-Meier analysis, patients of IND-AD demonstrated comparable 180-day TFS of that of INF-AD (p = 0.79), but significantly worse TFS than those of all the other PFs (p = 0.02). However, none of the known prognostic parameters including MELD, MELD-Na, CLIF-C OF scores, CLIC-C ACLF scores differentiated the 3 groups. Compared to cases of all the other PFs, those of IND-AD and INF-AD shared similar clinical features including a significant lower level of serum albumin (p = 0.07; 0.008, respectively) and tended to have higher baseline creatinine levels. Compared to cases of INF-AD, those of IND-AD tended to complicate with hepatic encephalopathy (p = 0.11), and to suffer from subsequent episodes of Grade 1–3 ACLF within 3 months (p = 0.09).

Conclusion: IND-AD shares similar clinical features with INF-AD, including worse 180-day transplant-free survival, lower serum albumin and more impaired renal function. Whether any infection that is not easily identifiable (such as fungal infection) or hypoalbuminemia might be therapeutic targets in decompensation of LC warrants more investigations in the future.

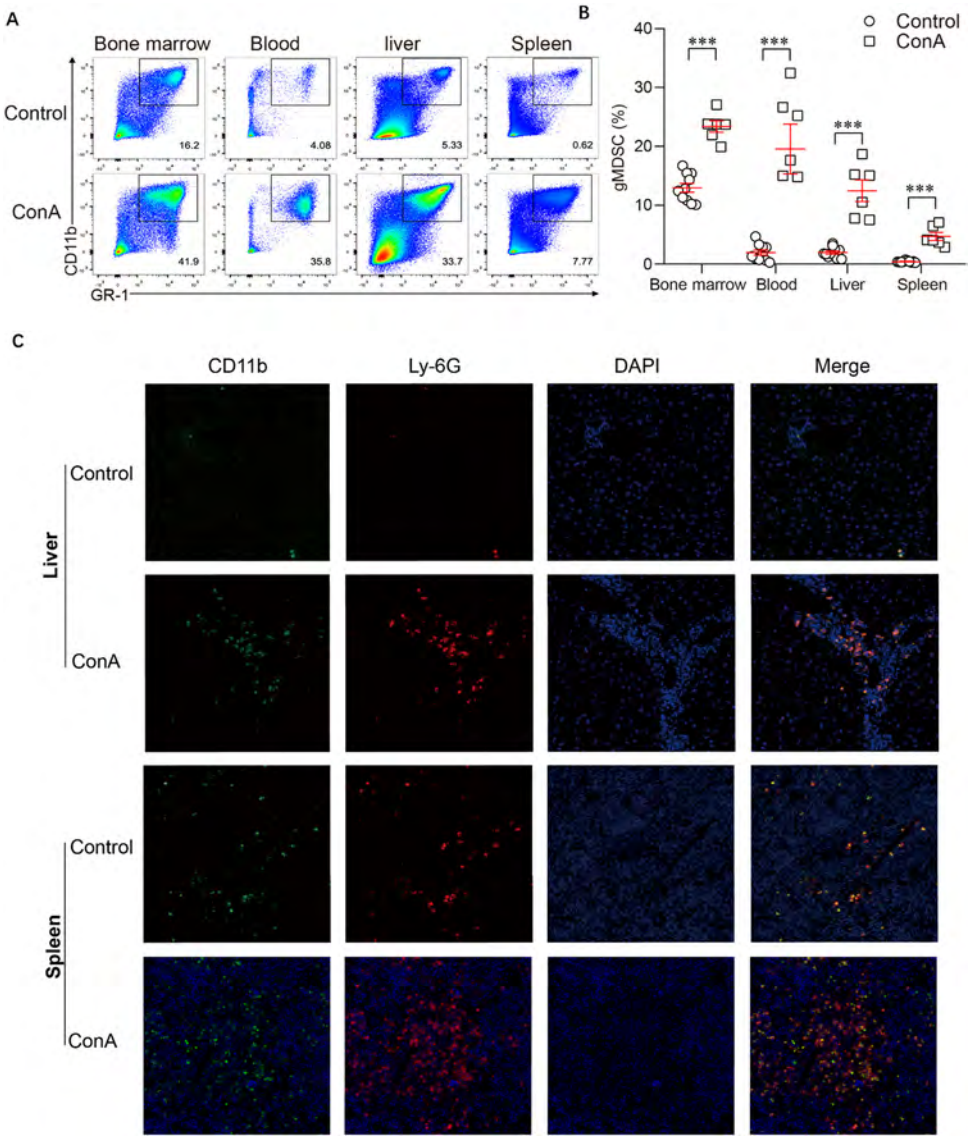

Figure 1: (abstract: FRI213): The percentage of gMDSC in peripheral blood, liver, spleen and bone marrow were markedly increased in ACLF mouse model induced by Concanavalin (n = 5) compare to the control group (normal saline, n = 10).

FRI213

Granulocytic myeloid-derived suppressor cells contribute to HBV-related acute-on-chronic liver failure infection and mortality by inducing T cell exhaustion

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Background and Aims: Hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) is characterized by susceptibility to infection and T-cell immune exhaustion. Studies have shown that granulocytic myeloid-derived suppressor cells (gMDSC) may lead to persistent HBV infection by suppressing T-cell function. However, it is unclear whether gMDSC could lead to T-cell immune exhaustion and infection in HBV-ACLF patients by inhibiting T-cell function.

Method: The blood and liver samples were collected from healthy subjects, chronic hepatitis B (CHB) and HBV-ACLF patients admitted to Huashan hospital and the first hospital of Quanzhou. ACLF mouse model was established by continuous injection of Concanavalin for 5 times (15 mg/Kg, every other day). The frequency of gMDSC in human peripheral blood mononuclear cells and intrahepatic immune cells, and in mouse peripheral blood, liver, spleen and bone marrow, were detected by flow cytometry and immunofluorescence. The expansion of gMDSC were detected by adding recombinant cytokines or corresponding inhibitors. The effects of gMDSC on proliferation and cytokines secretion of T-cells were observed upon co-culturing purified gMDSC and PanT cells. Anti-indoleamine 2,3-dioxygenase (IDO) was used to determine whether gMDSC could inhibit the function of T-cells through IDO signal pathway.

Results: The frequency of human gMDSC (HLA-DR$^-$CD33$^+$CD11b$^+$CD14$^-$CD15$^+$) in circulation and intrahepatic immune cells of HBV-ACLF patients were significantly increased and positively correlated with severity of disease, prognosis and infection. Moreover, the percentage of gMDSC (GR-1$^+$CD11b$^+$Ly6C$^-$Ly6G$^+$) in peripheral blood, liver, spleen and bone marrow of ACLF mouse model were also markedly increased compare to the control group.

Immunofluorescence results showed that the number of gMDSC cells in the liver tissues of HBV-ACLF patients and the liver and spleen tissues of ACLF mouse models were significantly increased. TNF-α facilitate to the expansion of gMDSC, while blocking or neutralizing TNF-α signalling pathways decrease the frequency of gMDSC. Importantly, HBV-ACLF patient-derived gMDSC inhibited T-cell proliferation and interferon-γ secretion. Mechanistically, neutralization of IDO blunted the inhibition effects of gMDSC on T-cell.
Conclusion: gMDSC were compensatory increased, leading to the gradual decline of T-cell function until exhaustion, which may weaken the ability of removing pathogen, and eventually contribute to infection and aggravate HBV-ACLF patients' death. This study is helpful to elucidate the pathogenesis of HBV-ACLF and provide a new drug target.

Fibrosis

FRI214

Baseline demographics and clinical characteristics of subjects enrolled in the phase 3 AURORA study of cenicriviroc for the treatment of liver fibrosis associated with non-alcoholic steatohepatitis

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Background and Aims: Approximately 10–20% of subjects with NAFLD have nonalcoholic steatohepatitis (NASH) with varying degrees of fibrosis. The severity of liver fibrosis significantly increases the risks of liver-related and all-cause morbidity and mortality. No treatments are approved for fibrotic NASH. Cenicriviroc, a novel, once-daily, oral, potent inhibitor of C-C chemokine receptor types 2 and 5, is currently in development for the treatment of liver fibrosis in adults with NASH.
Method: AURORA (NCT03028740) is an ongoing, global, Phase 3, multicentre, randomised, double-blind, placebo-controlled trial to evaluate a surrogate histology endpoint (improvement in fibrosis by ≥1 stage per NASH CRN classification AND no worsening of steatohepatitis) in Part 1 (~1200 subjects) and clinical outcomes (time to first occurrence of any adjudicated events of mortality, histologic progression to cirrhosis or specified liver-related events) in Part 2 (~2000 subjects overall). Adults with histologic diagnosis of NASH and Stage 2 or 3 liver fibrosis per NASH CRN are enrolled. Subjects with cirrhosis or other causes of chronic liver disease are excluded. We aim to describe the baseline demographics and clinical characteristics of subjects enrolled in AURORA.
Results: Approximately 6000 subjects were screened by the analysis date and 1122 were randomised, with histology criteria being the primary reason for screen failure. The majority of the randomised subjects were female (63%), white (90%), with a mean age of 54 years (SD: 11). The mean BMI was 36 kg/m^2 (SD: 7). Fifty one percent had type 2 diabetes mellitus; most commonly used treatments were biguanides (84%) and sulfonylureas (23%). Hypertension was present in 61% of subjects, and 35% were on statins; 42% had Stage 2 and 56% had Stage 3 fibrosis. Table 1 shows baseline laboratory parameters, including non-invasive fibrosis markers.

Table 1: Baseline laboratory data

Laboratory parameter	Mean	SD
ALP* (IU/L)	86.2	34.2
ALT* (units/L)	57.7	38.2
AST* (units/L)	45.5	28.1
Total bilirubin* (μmol/L)	8.23	4.84
Platelet count* (×10^9/L)	240.4	66.6
FIB-4**	1.5	0.7
APRI**	0.6	0.5
NFS**	−0.9	2.0

*Available for 1097 subjects at data analysis date; **Evaluable for 1091 subjects

Conclusion: AURORA is one of the largest ongoing Phase 3 trials in subjects with fibrosis due to NASH. Description of the demographics and clinical characteristics of subjects screened and enrolled in this study will help to further characterise this population and inform the design of future trials. Editorial assistance by Complete HealthVizion.

FRI215

Diagnostic accuracy of a pocket-size ultrasound device in identifying liver surface nodularity for fibrosis staging in chronic liver disease

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Background and Aims: In chronic liver disease fibrosis is the key prognostic factor. Liver biopsy, the reference standard for hepatic fibrosis assessment, is an invasive procedure with a small but significant risk of life-threatening complications. Many non-invasive tests have been evaluated as alternatives. Liver surface nodularity (LSN) is the highest-accuracy ultrasonographic sign to detect advanced liver fibrosis (F3-F4). Pocket-size Ultrasound Devices — with their small size, low cost and ease of use — have been assessed in several clinical settings, but never in CLD.
Our cross-sectional study evaluated PUD feasibility, reproducibility and accuracy in identifying LSN.
Method: Between September 2017 and January 2019 we enrolled all consecutive consenting adults referred for liver parenchymal biopsy. LSN was evaluated by 2 independent operators using PUD (Vscan® Dual Probe GE Healthcare, UK), and by an operator using standard GIUS. Transient elastography (TE) and liver biopsy were performed on all patients. PUD reproducibility was evaluated by κ coefficient.
PUD, GIUS and TE results were compared with histology (METAVIR). The estimated pre-test probability of severe fibrosis was 35%. Sensitivity, specificity, positive/negative likelihood ratios, and post-test probability were calculated
Results: For 72 patients (31 M, age 47 ± 28 years, NAFLD/NASH 35%, AIH 25%, PBC/PSC 14%, HBV/HCV 12%,, other 14%) PUD reproducibility (κ 0.82, 95% CI 0.68–0.96) and concordance between PUD and GIUS (κ 0.78, 95% CI 0.64–0.94) were excellent. In diagnosing F ≥ 3PUD achieved: 87% sensitivity, 91% specificity, LR+ 9.7, LR- 0.14, PPV 84%, NPV 93% against GIUS (95% sensitivity, 93% specificity, LR+ 13.5, LR-

0.05, PPV 88%, NPV 97%) and TE (67% sensitivity, 96% specificity, LR+ 16, LR- 0.35, PPV 89%, NPV 86%).

Variables	Cut off kPa	Sn %	Sp %	LR+	LR-	PPV %	NPV %	AUROC (95% CI)
Vscan	-	87	91	9.7	0.14	84	93	0.875 (0.78–0.94)
US	-	95	93	13.5	0.05	88	97	0.937 (0.85–0.98)
TE	10.3	67	96	16	0.35	89	86	0.967 (0-89–0.99)

Conclusion: PUD proved feasible, with excellent reproducibility. PUD performed very well in diagnosing advanced compensated CLD, and comparably to GIUS and TE. PUD is deployable as first-line screening to select patients for more invasive techniques, thus shortening clinical decision times.

FRI216

Combination of an acetyl CoA carboxylase inhibitor with therapeutics that promote fatty acid oxidation moderately improves efficacy in a preclinical NASH model

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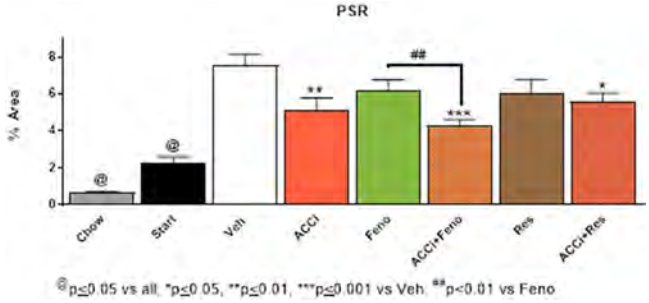
Background and Aims: Firsocostat, a liver-directed acetyl-CoA carboxylase inhibitor (ACCi) is currently being investigated in NASH patients with F3/F4 fibrosis. ACC simultaneously increases de novo lipogenesis and inhibits mitochondrial fatty acid oxidation (FAO) in hepatocytes. We have previously shown that ACC inhibition reduces fibrosis in a rat choline-deficient high-fat diet (CDHFD) model of NASH, partially via direct inhibition of hepatic stellate cell activation. In the current study, we assessed if increasing hepatocyte FAO, using either peroxisomal proliferator-activated receptor alpha (fenofibrate, Feno) or thyroid hormone receptor beta (Resmetirom, Res) agonists, could augment the anti-fibrotic efficacy of an ACCi.
Method: Male rats were fed CDHFD for 12 weeks and treated with Vehicle (Veh), 10 mg/kg ACCi, and 5 mg/kg Feno or 3 mg/kg Res, alone or in combination (combo) with ACCi, from week 6–12 (n = 15/group). Separate groups of rats were either maintained on normal chow or sacrificed after 6 weeks on CDHFD (Start). Hepatic fibrosis was assessed by quantitative morphometry of liver sections after picrosirius red (PSR) staining or alpha smooth muscle actin (αSMA) immunohistochemistry. Additional end-points measured included plasma non-invasive markers of fibrosis and total liver triglycerides (TG).
Results: CDHFD significantly increased hepatic PSR and αSMA area at 6 weeks (2.3 and 0.9% respectively) and 12 weeks (7.6 and 2.8% respectively) vs chow ($p < 0.05$). Among the monotherapy arms, ACCi reduced PSR and αSMA by 32% ($p = 0.01$) and 48% ($p = 0.001$), respectively vs Veh, while Res significantly reduced αSMA by 33% ($p = 0.04$) but not PSR. Compared to Veh, the ACCi/Feno combo reduced PSR and αSMA by 43% ($p = 0.0001$) and 59% ($p = 0.0001$), respectively, and the ACCi/Res combo by 26% ($p = 0.02$) and 57% ($p = 0.004$), respectively. The trend for improved efficacy in the combo groups compared to ACCi alone were not statistically significant. Similar treatment responses were observed in plasma markers of fibrosis with ACCi/Res combo reducing TIMP 1 and CK18 (M30) beyond ACCi alone ($p < 0.05$). None of the treatments (single agent or combo) changed total liver TG.



Conclusion: ACC inhibition reduced fibrosis progression in a preclinical model of NASH. Increased hepatocyte FAO with Res or Feno did not reduce fibrosis progression, however when used in combination with an ACCi, these therapeutics moderately increased anti-fibrotic efficacy.

FRI217

PBI-4050 promotes hepatic stellate cell deactivation by shifting energy metabolism

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Background and Aims: The establishment and progression of liver fibrosis is the best predictive factor of long-term outcome in NAFLD and NASH. One of the most important features in the establishment of liver fibrosis is unquestionably the activation of Hepatic Stellate Cells (HSCs). PBI-4050, a GPR40 agonist and GPR84 antagonist, and a lead drug candidate in the treatment of fibrotic-related diseases, has previously demonstrated strong anti-proliferative activity towards HSCs. In the present study, we investigated the mechanism by which PBI-4050 reverses HSCs proliferation and activation.
Method: *In vitro* culture of primary human HSCs were used to evaluate the effects of PBI-4050. A Seahorse XFe-96 analyzer was used to measure the effects of PBI-4050 on mitochondrial respiration and glycolysis. The expression profile of genes involved in glucose/fatty acid metabolism, fibrosis and inflammation was determined on HSCs activated by TGF-β1. The gene expression profile of PBI-4050-treated cells was compared to retinoic acid, an agent known to promote HSC deactivation.
Results: In the presence of glucose, levels of mitochondrial respiration and glycolysis were reduced, suggesting that PBI-4050 could shift the energy balance towards fatty acid oxidation (FAO). At the basal state, PBI-4050-treated HSCs harbored a quiescent-like energy phenotype characterized by a decreased level of intracellular ATP. Moreover, in TGF-β-activated HSCs, genes involved in FAO, such as CPT1, CPT2, ACLS1 and PDK4, were upregulated by PBI-4050, while genes involved in fibrosis and inflammation (α-SMA, CTGF, IL-8) were greatly reduced. Finally, expression of the lipid droplet marker perilipin-2, associated to HSC quiescent phenotype, was upregulated by PBI-4050.
Conclusion: These results indicate that PBI-4050 restores HSC quiescent-like phenotype by shifting energy metabolism towards FAO and could be a potential therapy for the treatment of liver fibrosis.

FRI218

Diagnostic accuracy of WFA+ – M2BP for significant hepatic fibrosis determined by MR elastography

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Background and Aims: Accurate evaluation of significant hepatic fibrosis is crucial for management of patient with chronic liver disease. We investigated the diagnostic performance of novel fibrosis glycobiomaker Wisteria floribunda agglutinin-positive Mac-2-binding protein (WFA+-M2BP) for evaluation of significant fibrosis diagnosed by MR elastography (MRE) in subjects with chronic liver disease and healthy subjects.
Method: A total of 490 subjects (mean age: 59, range: 33–80) who underwent serological tests for WFA+-M2BP were enrolled. 245 subjects with chronic liver disease underwent MRE and propensity score matched 245 healthy subject were analysed. The value of MRE 3.6 or above was considered as significant fibrosis. Clinical data were compared with other noninvasive markers (aspartate transaminase/alanine aminotransferase ratio (AAR), aspartate transaminase to platelet ratio index(APRI), fibrosis-4(FIB-4) index) for estimating significant fibrosis using receiver operating characteristic (ROC) analysis.
Results: Serum WFA+-M2BP level of health subjects, chronic liver disease without significant fibrosis and with significant fibrosis was 0.55 ± 0.32, 1.12 ± 0.76, 5.16 ± 5.39, respectively ($p < 0.001$). It was not significantly difference between sex, however, some difference between the cause of the chronic liver disease. The area under the ROC curves for significant fibrosis using cutoff value of 1.08 was 0.916 (95% CI: 0.888–0.939) was comparable to that using FIB-4 index of 0.885 (95% CI : 0.854–0.912) ($p = 0.202$), and superior to other surrogate marker, including AAR (0.793, $p < 001$) and APRI (0.870, $p = 0.045$).
Conclusion: WFA+-M2BP is a reliable noninvasive surrogate marker for predicting the significant hepatic fibrosis for chronic liver disease.

FRI219

ZLN005, PGC-1? activator, induces oxidative phosphorylation and lipogenesis in myofibroblasts to reverse liver fibrosis

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Background and Aims: Metabolic alterations are responsible for the activation of hepatic stellate cells (HSCs), which leads to liver fibrosis. PGC-1α, the central regulator of oxidative phosphorylation (OXPHOS) and lipogenesis, is closely related to cell fate. We aim to explore the mechanisms underlying therapeutic potentials of PGC-1α signaling in *mdr2* knockout-induced liver fibrosis model.
Method: Immunohistochemical staining and q-PCR analysis were performed to identify the expression of glucose and lipid metabolic genes, as well as PGC-1α in liver samples of patients with cirrhosis and $mdr2^{-/-}$ mice. Myofibroblasts were isolated from fibrotic liver tissues and administrated with PGC-1α vectors or PGC-1α activator, ZLN005, to determine the anti-fibrotic effects and the switch of glucose and lipid metabolism by measurement of glucose uptake ability, oxygen consumption rate, lactate accumulation and lipid staining, as well as expression of key metabolic enzymes. Moreover, $mdr2^{-/-}$ mice developed liver fibrosis spontaneously were administrated with ZLN005 to explore the therapeutic effects.
Results: PGC-1α was downregulated in fibrotic regions compared with normal liver tissues, accompanied with the increasing expression of glycolytic and fatty acid oxidation (FAO) enzymes. Furthermore, transfection of PGC-1α vectors or ZLN005 could reverse the fibrotic phenotype of myofibroblasts and promote the switch of glucose metabolism from glycolysis to OXPHOS and lipid metabolism from FAO to lipogenesis. Mechanically, PGC-1α overexpression increased NAD+/NADH ratio, subsequently activated sirtuin1 and deacetylated PGC-1α, which formed positive loop to constitutively activate PGC-1α signaling. In addition, ZLN005 therapeutically alleviated liver fibrosis in $mdr2^{-/-}$ mice models by modulating metabolic pathways.
Conclusion: This study demonstrated a two-arm mechanism on metabolic regulation by which PGC-1α accelerated fibrosis resolution. PGC-1α activator ZLN005 might be considered as a potential anti-fibrotic treatment.

FRI220

Prevalence of significant hepatic fibrosis using magnetic resonance elastography in a health check-up clinic population

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Background and Aims: Significant hepatic fibrosis is associated with higher mortality. However, data on the prevalence of liver fibrosis in the general population are scarce, owing to the fact that liver biopsy is neither feasible nor ethical in the community setting. Using magnetic resonance elastography (MRE), we investigated the prevalence of significant fibrosis in a community-based cohort.
Method: We enrolled 2,170 participants at our health check-up clinic between 1/2015 to 5/2018, all of whom had MR with chemical shift technique and MRE. The primary study objective was the prevalence of liver fibrosis defined as F2 or F3 by MRE. For generalization, sex- and age-standardized prevalence estimates were calculated based on the Korean Statistical Information Service (KOSIS) in 2015–2018.
Results: The prevalence of F2 (≥3.0 kPa) and F3 fibrosis (≥3.6 kPa) in the overall cohort was 5.1% and 1.3%, respectively (sex-and age-adjusted prevalence of 3.8% and 1.3%). NAFLD prevalence (>5% fat fraction) was 20.8% in the average risk population (after excluding alcohol use and viral hepatitis), and the prevalence of significant and advanced fibrosis in NAFLD participants was 7.5% and 1.1%, respectively. The prevalence of DM was 7.7% in the overall cohort, with significant fibrosis in 13.7% and advanced fibrosis in 4.8%. In participants with fatty liver (of any etiology) plus diabetes, 27.5% had ≥F2 and 7.2% ≥F3. Multivariate analyses indicated that older age, lower platelet count, higher AST/ALT ratio, diabetes, and fatty liver were independently associated with significant fibrosis.

Table: Factors associated with significant hepatic fibrosis (≥F2, 3.0 kPa) using MRE (N = 2,170)

	Univariate		Multivariate	
	OR	95% CI	OR	95% CI
Male (%)	2.15	1.15–4.06	2.05	0.85–4.95
Age (years)	1.05	1.02–1.07	1.04	1.02–1.07
BMI (kg/m2)	1.08	1.02–1.15	0.95	0.82–1.09
Waist (cm)	1.03	1.01–1.06		
Platelet (10^9/L)	0.99	0.99–1.00	0.99	0.99–1.00
AST/ALT	1.03	0.60–1.77		
Triglycerides (mg/dL)	1.00	0.99–1.00		
Total cholesterol (mg/dL)	1.00	0.99–1.01		
HDL-cholesterol (mg/dL)	1.00	1.00–1.01		
LDL-cholesterol (mg/dL)	1.00	1.00–1.01		
Fat mass (kg)	1.04	1.01–1.07	1.03	0.96–1.11
Muscle mass (kg)	1.01	0.99–1.04		
ASM (kg)/height(m)2	1.17	1.00–1.37	1.07	0.85–1.36
Glucose (mg/dL)	1.02	1.01–1.03		
Insulin (μUmL)	1.08	1.05–1.11	1.07	1.03–1.12
Diabetes	3.49	2.14–5.70	2.83	1.67–4.81
Hypertension	1.52	1.03–2.26	1.07	0.69–1.66
Fatty liver on MR	2.46	1.67–3.62	1.77	1.12–2.80

Conclusion: In a health check-up clinic setting, the prevalence of significant and advanced fibrosis was 5.1% and 1.3% in (sex-and age-adjusted prevalence of 3.8% and 1.3%, respectively) and increased three- to four-fold with diabetes.

FRI221

GLI1, but not smoothened-dependent, signaling in hepatic progenitor cells promotes a ductular reaction, which aggravates liver fibrosis

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Background and Aims: Ductular reaction (DR) is pathologically recognized as bile duct hyperplasia and is commonly observed in various liver disorders. It is still unclear, however, whether DR promotes liver fibrosis via elevated bile duct mass and cholangiocyte activation, or DR protects the liver during injury by enhancing liver regeneration. We studied detailed mechanisms and the functional roles of DR in liver fibrosis.
Method: Liver samples of 144 chronic hepatitis B patients were obtained from biopsy. Masson staining and cytokeratin19 immunostaining were performed to observe the collagen deposition and ductular reaction. Fibrosis was induced in rats via two kinds methods, including carbon tetrachloride combined with 2-acetylaminofluorine and bile duct ligation *in vivo*. Meanwhile, GANT61, a Gli1 inhibitor was intraperitoneal injected to investigate the therapeutic efficacy on DR and liver fibrosis progression. *In vitro* hepatic progenitor cells (HPCs) were treated with sodium butyrate to provide direct evidence for differentiation towards cholangiocytes, meanwhile with or without GANT61, small interfering RNAs against Gli1 (siRNA-Gli1) or lentivirus vector overexpressing Gli1 (LV-Gli1).
Results: The results of patients' sample showed that DR was notably enhanced with the severity of liver fibrosis and closely correlated with collagen deposition. The results in both models *in vivo* showed that a large number of hepatic progenitor cells were activated and proliferated, and differentiated to cholangiocytes (DR) to promote the fibrosis progression, and upregulation of Gli1 was observed during a DR. While inhibiting the Gli1 expression suppressed DR and fibrosis progression. *In vitro*, we found that Gli1, but not Smoothened-dependent signaling was activated during differentiation of HPCs into fibrogenic cholangiocytes. And Gli1 knock-down can directly inhibit this process.
Conclusion: DR plays a key role in pathogenesis of aggravating liver fibrosis. Gli1, but not Smoothened-dependent, signaling directs differentiation of HPCs to fibrogenic cholangiocytes and promotes liver fibrosis progression suggesting that DR and Gli1 may be potential targets to treat liver fibrosis.

FRI222

Enigma proteins control YAP1 related mechano-transduction in hepatic stellate cells

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Background and Aims: Liver fibrosis is defined by dysregulated extracellular matrix (ECM) deposition by hepatic stellate cells (HSCs). In response to liver injury HSCs adopt an activated proliferative, migratory, and contractile myofibroblast phenotype. Increases in organ stiffness occur rapidly after liver injury[1 2], and are necessary for HSC activation. Mechano-transduction caused by the stiffened fibrotic ECM then drives further activation of HSCs. Yes Associated Protein (YAP) 1 is a key mechano-regulator of HSC activation and fibrotic gene expression[3]. It remains unclear how mechanical force from outside the cell triggers the nuclear translocation of YAP1, allowing YAP1 to drive fibrotic gene expression. We propose that mechano-activation of YAP1 in HSCs is regulated by the enigma protein family members PDLIM5 and PDLIM7[4].
Method: Human liver tissue was from the Manchester Biobank (ethical approval NW1260/22). Primary human or mouse HSCs were isolated using standard liver perfusion, digestion and density gradient centrifugation. Enigma family gene and protein expression was characterized in immortalized human HSCs (LX-2 cells) and primary HSCs by qPCR, western blot (WB) and immunocytochemistry (ICC). LX-2 s and primary HSCs were grown on hyrdrogel substrates of varying stiffness to model mechanical ECM changes. LX-2 cells were transfected with plasmids expressing flag tagged PDLIM5 or 7 for immunoprecipitation experiments. siRNA was used to disrupt Enigma protein expression in LX-2 cells and verified by qPCR, western blot and ICC.
Results: PDLIM5 and 7 expression was confirmed by PCR, western blot and ICC in LX-2 cells and primary HSCs. Lx-2 cells and primary HSCs grown on soft substrates had altered Enigma protein and YAP1 localization. Stimulation of LX2 cells with TGFβ (2 ng/ml) for 24 hrs significantly increased expression of PDLIM5 and PDLIM7. Immunoprecipitation experiments show that enigma proteins physically interact with YAP1 in LX-2 cells. siRNA knock down of *PDLIM5* or *PDLIM7* reduced the expression of fibrotic genes including *Acta2*, and was accompanied by increased cytoplasmic localization of YAP1.
Conclusion: The current study reveals a new mechanism for YAP1 activation in HSCs. The Enigma proteins PDLIM5 and PDLIM7 are expressed in LX-2 cells and culture activated primary human HSCs. Knockdown of Enigma protein expression reduced fibrotic gene expression and YAP1 activation. Understanding hippo independent mechanisms of YAP1 activation in HSCs may reveal novel targets for urgently needed anti-fibrotics.

References

1. Olsen AL et al. *Am J Physiol Gastrointest Liver Physiol* 2011 doi: 10.1152/ajpgi.00412.2010
2. Georges PC et al. *Am J Physiol Gastrointest Liver Physiol* 2007 doi: 10.1152/ajpgi.00032.2007
3. Martin K and Pritchett J et al. *Nat Commun* 2016 doi: 10.1038/ncomms12502
4. Elbediwy A et al. *J Cell Sci* 2018 doi: 10.1242/jcs.221788

FRI223

Growth differentiation factor 11 attenuates liver fibrosis via expansion of liver progenitor cells

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Background and Aims: Liver fibrosis and cirrhosis resulting from long-standing liver damage represent a major health care burden worldwide. Members of the transforming growth factor β (TGF-β) family have been shown to play a pivotal role in fibrogenesis of the liver as well as multiple other organs. Growth differentiation factor (GDF) 11, a member of TGF-β family, has been recently investigated for its role in the rejuvenation of aging organs. However, the function of GDF11 in liver fibrosis has remained elusive. Here, we investigated the expression and function of GDF11 in chronic liver disease.
Method: We analyzed the expression of GDF11 in patients with liver fibrosis, in a mouse model of liver fibrosis and in hepatic stellate cells (HSCs) as well as in other liver cell types. The functional relevance of GDF11 in toxin- and cholestasis-induced mouse models of liver fibrosis was examined by *in vivo* modulation of *Gdf11* expression using adeno-associated virus (AAV) vectors. The effect of GDF11 on leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5)+ liver progenitor cells was studied in mouse and human liver organoids culture. Furthermore, *in vivo* depletion of LGR5+ cells was induced by injecting AAV vectors expressing diptheria toxin A under the transcriptional control of *Lgr5* promoter.

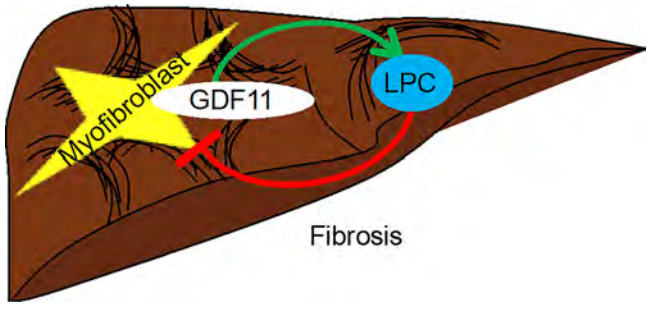

Figure: The expression of GDF11, mainly secreted by myofibroblasts, is enhanced upon chronic liver injury. The overexpression of GDF11 in injured liver promotes expansion of LGR5+ liver progenitor cells, which in turn attenuate liver fibrosis.

Results: We show that expression of GDF11 is upregulated in patients with liver fibrosis and in experimentally induced murine liver fibrosis models. Furthermore, we found that therapeutic application of GDF11 mounts a protective response against fibrosis by increasing the number of LGR5+ progenitor cells in the liver.
Conclusion: Collectively, our findings uncover a protective role of GDF11 during liver fibrosis and suggest a potential application of GDF11 for the treatment of chronic liver disease.

FRI224

The IL-17a and IL-22 cytokines like triggers of human liver fibrosis

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Background and Aims: IL-17A and IL-22 are both related to liver fibrosis. Their role is dual, depending on the type of the model that was used. IL-17A is considered to be a profibrotic cytokine while IL-22 shows anti-fibrotic properties in the mice models of acute liver diseases. Here, we analyzed IL-17A and IL-22 secretion in human liver tissue samples of different fibrotic stages, as well as their influence on fibrotic markers expression in the model of human liver slices culture.
Method: Human fibrotic liver samples (F0-F4 fibrosis stage) were collected after liver resection. Human precision-cut liver slices of 350 µm were stimulated with different cytokines (IL-17A, IL-22, TGF-beta) for 48 hours, fibrotic markers (alfa-SMA, MMP-2, MMP-9, TIMP-1) were assessed by western blotting and Elisa. **I**ntrahepatic liver infiltrating immune cells was extracted from post-surgery liver samples, stimulated and analyzed by flow cytometry. Thirty human liver samples after liver resection were analyzed for IL-17A, IL-22, TGF-beta expression.
Results: Here, we report an unexpected raise of IL-17A and IL-22 cytokine concentration in human liver tissue samples (F0-F1, F2) compared to advanced fibrosis (F3-F4), as well as their significant correlation. On the other side, the TGF-beta secretion was higher in advanced fibrotic stages. Liver infiltrating $CD3^+CD4^+$ lymphocytes and MAIT cells were the principal source of IL-17A and IL-22 among lymphoid cells. We identified much stronger secretion of INF-gamma in the liver tissue compared with blood samples of the same patient. In addition, the liver tissue from mild fibrotic samples had significantly greater infiltration by the $CD45^+CD3^+$TCRValfa7.2 cells than the liver samples with advanced fibrotic stages. In the second time, we stimulated human liver slices culture by IL-17A, IL-22 or TGF-beta. We observed that IL-17A promotes IL-6 production in the liver, as well as MMP-2, MMP-9 and TIMP-1 production. However, IL-22 didn't induce MMP-9 and TIMP-1 expression during 48 h of stimulation neither alone nor in presence of TGF-beta. IL-17A and IL-22 both were capable to stimulate alfa-SMA synthesis, the principal marker of stellate cells activation contributing either to liver regeneration or to liver fibrosis.
Conclusion: The strong expression of IL-17A and IL-22 in earliest fibrotic stages as well as the increased expression of fibrotic markers should highlight the importance of these cytokines to trigger human liver fibrosis.

FRI225

Fib-4 score for assessment of liver fibrosis is useful in general practice

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Background and Aims: Chronic liver inflammation, mainly due to non-alcoholic fatty liver disease (NAFLD), leads to fibrosis which may progress to cirrhosis and cancer. Early detection of hepatic fibrosis is a challenge and should be performed by general practitioners (GP). The

FIB-4 score is a non-invasive fibrosis scoring test based on routine laboratory parameters and have been shown to rule in/rule out significant fibrosis (1).

Objectives: 1) Measure by FIB4 score the prevalence of significant liver fibrosis in adults consulting a GP; 2) compare this tests to others APRI, NAFLD Fibrosis Score (NFS), Fibrometer V3G; 3) explore the prevalence of main risk factors (obesity, diabetes, alcohol consumption, hypertension) and their link with fibrosis scores; 4) describe the causes of liver disease.

Method: Over a 6-month period, from 10/01/2018 to 03/31/2019, 40 GPs from the French Alpes Maritimes area offered all their 45 to 79-year-old primary care patients, without known liver pathology and outside emergency, liver fibrosis screen via simple blood test allowing calculation of the non-invasive fibrosis scores. New thresholds for FIB4 and NAFLD fibrosis score were used in patients aged >65 years (2).

Results: Among the 2121 patients included (sex ratio M/F 0.61, mean age 62 years), 54% had a BMI>25 kg/m², 13% alcohol consumption >100 g/week, 10% diabetes and 29% hypertension. Increased ASAT rate was found in 6.8%, ALAT in 6.1% and GGT in 15% of cases. The prevalence of significant hepatic fibrosis defined as a FIB4≥1.3 (for <65year) and ≥2 (for >65 years) was 19.1% [95%CI 17, 5–20.9%]. By comparison, prevalence was at 0.28% [0.09–0.65%] by the APRI test, 16.8% [15.0–18.5%] by the NFS score defined as NAFLD ≥−1.455 (for <65 years) and ≥0.12 (for ≥65 years), and 8.2% [6.9–9.6%] by the Fibrometer V3G. Significant correlation was found between the positivity of FIB4, NFS, Fibrometer V3G and hepatic risk factors (obesity, diabetes, alcohol). Among the 406 patients with significant FIB4 score, GPs defined the cause of liver damage in 65% of cases: NAFLD 97, alcohol 48, both 24, other 24 cases. Specialized advice was requested for 65/406 patients. At the time of writing this abstract, 62/65 patients had interpretable hepatic stiffness measurements: 13 (21%) had an elasticity score >7 Kpa with a fibrosis stage F2 for 9, F3 for 2 and F4 for 2. An hepatic risk factor was found in all patients with elasticity >7 Kpa and in only 42% of patients with elasticity <7 KPa ($p < 0.05$).

Conclusion: Liver fibrosis was suspected by FIB4 score in 19.1% patients without known hepatic pathology, who consulted a GP. A liver stiffness >7 KPa was found in 21% of the FIB4 identified patients. The detection of significant fibrosis by a simple blood test allowed the GP to recognize a chronic liver disease and to define its cause in 2/3 of cases.

References

1. Xiao et al. *Hepatology* 2017; 66(5):1486–1501.
2. Mc Pherson et al. *Am J of Gastroenterology* 2017;112:740–51.

FRI226

Analysis of PNPLA3 SNP variants in human hepatic stellate cells in 3D human liver extracellular matrix scaffolds reveals key PNPLA3-dependent pro-fibrogenic features

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Background and Aims: The I148M variant of the Patatin-like phospholipase domain-containing 3 (PNPLA3) protein is the most robustly validated risk locus for the fibrogenic progression of chronic liver diseases. This study aimed to investigate a comprehensive genetic background of primary human Hepatic Stellate Cells (hHSC) genotyped for I148M PNPLA3 variants and its impact on hHSC profibrogenic behaviour.

Method: Primary hHSC were isolated (n = 23 donors) and cultured in 2D, then genotyped for PNPLA3(I148M) variants CG/GG. RNAseq data was analysed on 3 donors/genotype with Ingenuity pathway analysis (IPA). Cell behaviour of PNPLA3(WT) hHSC and PNPLA3(I148M) hHSC was evaluated in 3D decellularized scaffolds from human healthy and cirrhotic liver. Cells were cultured for 13 days and stimulated 3 × 48 h with TGFbeta1. QRT-PCR and RT Profiler array for human ECM and adhesion molecules was performed.

Results: IPA linked PNPLA3(I148M) hHSC variant to pathways related to cancer, gastrointestinal diseases and connective tissue disorders including "caveolar-mediated endocytosis," "triacylglycerol biosynthesis" and "corticotropin releasing hormone signalling." Comparing PNPLA3(I148M/CG) to PNPLA3(WT), the top dysregulated upstream effector was the oxidative stress-related kinase GSK3. A possible derangement of intracellular anti-oxidant response was also suggested by QPCR on 3D cultured hHSC, with decreased or absent expression of VARS2, a mitochondrial enzyme, GSTT1, a Glutathione-S-Transferase and CLEC3B (GSK3 downstream pathway) in PNPLA3 (I148M) hHSC compared to PNPLA3(WT) hHSC with/without TGFB1 treatment. RT profiler of 84 genes related to ECM and adhesion molecules showed an increased activation of PNPLA3(I148M) hHSC compared to PNPLA3(WT). Striking differences in the expression of integrin subsets, MMPs and ECM components was found comparing PNPLA3(148M) to PNPLA3(WT) hHSC cultured on healthy scaffolds, highlighting a more aggressive pro-fibrogenic phenotype of HSC carrying the mutation. The differences were more pronounced in hHSC cultured in cirrhotic scaffolds or stimulated with TGFB1.

Conclusion: This is the first study dissecting at the cellular level the profibrogenic mechanisms associated to PNPLA3 variants in hHSC employing an innovative 3D culture system recapitulating the ECM microenvironment of normal and cirrhotic human liver. The results indicate that hHSC carrying variants of PNPLA3(I148M) have a more aggressive profibrogenic phenotype also in reason of a dysregulated oxidative stress response.

FRI227

An HSV-TK / valganciclovir mouse model enables the study of fibrocytes in liver fibrosis

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Background and Aims: Bone marrow-derived fibrocytes, defined as spindle-shaped, $CD45^+/Col1^+$ cells, have been implicated in the pathogenesis of fibrotic diseases of the kidney, lung, heart, and liver. Previous studies demonstrated the specific proliferation and infiltration of fibrocytes into the injured liver. However, prior investigations were limited to cell culture or fate-tracing approaches. We aimed to establish a specific depletion of fibrocytes in a murine model to study their contribution to chronic-toxic liver fibrosis.

Method: Transgene C57BL/6 mice expressing a herpes simplex virus thymidine kinase (HSV-TK) under the control of a collagen type I promotor were generated. Bone marrow of transgene mice was transplanted into lethally irradiated wild type mice of the same

genetic background (n = 16 per group, controls received wild type bone marrow). After 4 weeks of reconstitution, thioacetamide (TAA, 300 mg/l) and valganciclovir (8.3 mg/l) were administered via drinking water for 18 weeks. Mice were sacrificed and RNA *in situ* hybridization was applied. Fibrocytes were identified in liver sections by the simultaneous expression of *Ptprc* (CD45) and *Col1a1* (collagen type I alpha chain) mRNA transcripts. Hepatic hydroxyproline content and serum alanine aminotransferase (ALT) levels were measured.

Results: RNA *in situ* hybridization visualized fibrocytes in mice which received wild type bone marrow. The transplantation of transgene bone marrow lead to a marked reduction of fibrocytes. The treatment was well tolerated presenting no signs of unwanted side effects. Mice of both groups gained weight steadily, liver histology showed a marked perilobular fibrosis comparable to preceding experiments involving TAA-induced liver fibrosis. Immunohistochemical stainings of CD68, F4/80, Ly6G, and myeloperoxidase demonstrated an unchanged pattern of distinct leucocytes in the liver. The expression of alpha-SMA^{+} myofibroblasts was unaffected by the fibrocytes depletion, indicated by western blot, RT-qPCR and immunohistochemistry, too. Both hepatic hydroxyproline content (381 vs. 413 µg/g liver; p = 0.033) and serum ALT levels (89 vs. 115 U/l; p = 0.049) were significantly reduced in consequence of the fibrocyte ablation.

Conclusion: The HSV-TK/Valganciclovir model allows for a specific depletion of bone marrow-derived fibrocytes, enabling new approaches to study this unique cell type. Our results, indicating an attenuation of fibrogenesis, emphasize the need to elaborate the biology of fibrocytes in liver fibrosis.

FRI228

Factors predicting liver histological changes under long-term follow-up chronic hepatitis C patients treated with pegylated-interferon-alpha plus ribavirin

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Background and Aims: The study aims to evaluate whether sustained viral response (SVR) and other factors predict liver histological changes under long-term follow up in chronic hepatitis C (CHC) patients receiving pegylated interferon (pegIFN)-alpha and ribavirin.

Method: From December 2005 to February 2017 at our hospital, 102 non-previously treated CHC patients were prospectively enrolled to receive pegIFN-alpha plus ribavirin and undergo long-term follow-up thereafter. To assess hepatic histological status, all patients received liver biopsy at treatment initiation and were invited to undergo second biopsy at the end of follow up.

Results: Only 18 patients failed to receive follow-up biopsy. In patients receiving paired biopsies (n = 84), mean duration between biopsies is 6.71 ± 1.43 years. SVR does not predict fibrosis regression [odds ratio (OR) = 1.606, p = 0.335] or stabilization (OR = 1.266, p = 0.627) in univariate analysis and insignificantly correlates with fibrosis progression (OR = 0.664, p = 0.653) in multivariate analysis. Conversely, pretreatment fibrosis stage ≥2 (F ≥ 2) independently predicts fibrosis regression (OR = 5.135, p = 0.005) and correlates with fibrosis stabilization (OR = 0.191, p = 0.003). Besides, decreased or permanently absent necroinflammatory activity (defined as activity response) is independently associated with fibrosis progression (OR = 0.068, p = 0.003). As for predictors of activity response, baseline glucose ≤ 105 mg/dL is the only factor showing significance in multivariate analysis (OR = 9.525, p = 0.022).

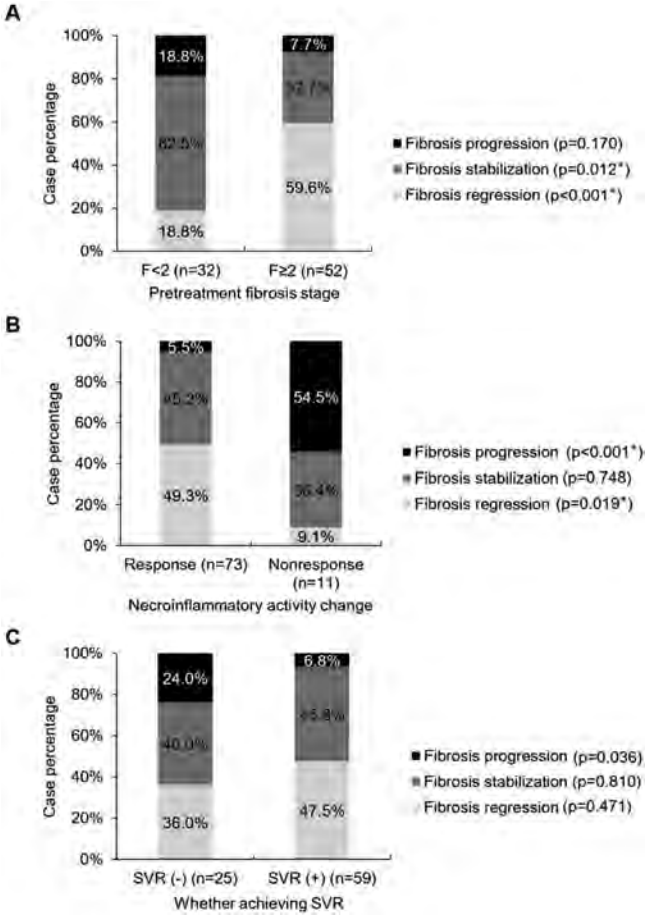

Figure: Percentage of cases presenting different fibrosis changes in hepatitis C patients (n = 84) divided by (A) pretreatment fibrosis stage (B) necroinflammatory activity change (C) whether achieving SVR.

Conclusion: Rather than SVR, pretreatment F ≥ 2 and activity response independently predict fibrosis changes under long-term follow up in CHC patients receiving pegIFN-alpha plus ribavirin. To achieve activity response, lowering serum glucose level before treatment is an effective method.

FRI230

TGF-beta3 plays a prominent role in murine parenchymal liver fibrosis

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Background and Aims: TGF-beta1 is considered the central profibrogenic cytokine that drives hepatic stellate cell/myofibroblast (HSC) activation in liver fibrosis. Less is known about TGF-beta2, and at best some controversial data exist on TGF-beta3. We therefore aimed to assess the profibrotic vs potential antifibrotic effect of TGF-beta3 in vitro and in vivo, with comparisons between TGF-beta1, TGF-beta2 and TGF-beta3.

Method: In vitro, recombinant TGF-beta1, TGF-beta2 and TGF-beta3 were added to murine 3T3 fibroblasts and human LX-2 HSC, followed by qPCR for major fibrosis-related transcripts (col1a1, acta2, pai1, timp1, pdgfb, mmp13, alk1, alk5, smad1/2/3/5/7/8, id2, bglyc, endogl,

tgfbr2). In vivo, C57BL/6 mice were treated with escalating doses of CCl4 for 6 weeks. Other groups were allowed to spontaneously regress for 1 or 4 weeks after 6 weeks of CCl4. Liver fibrosis was assessed by Sirius Red morphometry and hydroxyproline quantification. The gene expression of fibrosis and inflammation-related genes was assessed by qPCR.

Results: The 3 isoforms of TGF-beta highly significantly upregulated the expression of col1a1 and acta2 in 3T3 fibroblasts and HSC, while smad3 and smad8 as downstream mediators of the Alk5 and Alk1 pathway, respectively, id2, and the transcripts for the TGF-beta type II and III receptors (tgfbr2, bglyc) were equally downregulated. In contrast, smad7 as antagonists of the Alk5 pathway, and profibrogenic pai1 and timp1 (but also mmp13) were highly upregulated by the 3 TGF-beta isoforms. The 3 isoforms of TGF-beta equally (auto) induced TGF-beta1 and TGF-beta3 but not TGF-beta2. Notably, TGF-beta3 enhanced cola1a and acta2 transcription significantly more potently than TGF-beta1. In vivo, after 6 weeks of CCl4, transcript levels of TGF-beta1, TGF-beta2 and TGF-beta3 were upregulated 2.59 ± 0.48, 11.2 ± 2.75, and 13.0 ± 3.92 fold, respectively, reaching normal levels for TGF-beta1 already after 1 week of reversal, but remaining elevated 2–3 fold for TGF-beta2 and TGF-beta3 even after 4 weeks of reversal.

Conclusion: 1. TGF-beta3 is the most highly expressed TGF-beta isoform in murine parenchymal liver fibrosis; 2. TGF-beta3 robustly modulates fibrogenic signaling, mainly through Alk5, and is an equipotent and in some aspects more potent fibrogenic cytokine than TGF-beta1 and TGF-beta2; 3. This qualifies TGF-beta3 as an attractive target for antifibrotic therapies.

FRI231

MUDENG (mu-2 related death-inducing gene) overexpression accelerates liver fibrosis in carbon tetrachloride-induced cirrhosis

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Background and Aims: Liver fibrosis and its end-stage disease, cirrhosis, are major risk factors for hepatocellular carcinoma. MUDENG (Mu-2 related death-inducing gene, also known as AP5M1) is a gene which encodes a 490 amino acid protein initially reported to be involved in cell death of cytotoxic T cells, in tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-mediated anti-apoptotic signaling, and in trafficking of membrane vesicles. Recent advances in TRAIL signaling pathway presents a new target to achieve elimination of activated hepatic stellate cells, thereby reversing fibrosis. In this study, we developed a MUDENG transgenic mouse to further evaluate the role of MUDENG in inducing and potentially alleviating liver fibrosis.

Method: Eight 8-weeks-old male MUDENG transgenic mice and eight C57BL/6N male mice were injected with carbon tetrachloride (CCl_4) intraperitoneally twice weekly (40 μl/20–25 g, 50 μl/25–30 g body weight; 1:7 dilution with Olive oil). Livers were harvested at baseline for control and biweekly after intraperitoneal injection of CCl_4. The difference in the percent collagen area at baseline, 2, 4, and 6 weeks of the MUDENG transgenic mice and C57BL/6N mice was evaluated. Opensource software ImageJ (distributed by NIH) was used to calculate the collagen proportionate area of the liver after undergoing picoSirius red staining.

Results: The Ishak fibrosis grade of the MUDENG mice at baseline, week 2, 4, and 6 were 0, 1, 2, and 2, respectively. The Ishak fibrosis grade of the C57BL/6N mice at baseline, week 2, 4, and 6 were 0, 0, 1, and 1, respectively. The collagen proportionate area (CPA) at baseline in MUDENG and C57BL/6N mice were 0.36% and 0.38%, respectively ($p = 0.77$). The CPA at 2 weeks in MUDENG and C57BL/6N mice were 0.91% and 0.67%, respectively ($p = 0.03$). The CPA at 4 weeks in MUDENG and C57BL/6N mice were 2.51% and 1.29%, respectively ($p < 0.001$). The CPA at 6 weeks in MUDENG and C57BL/6N mice were 2.86% and 1.84%, respectively ($p < 0.001$). Greater expression of TGF-β throughout the life span in MUDENG transgenic mice compared to C57BL/6N was noticed.

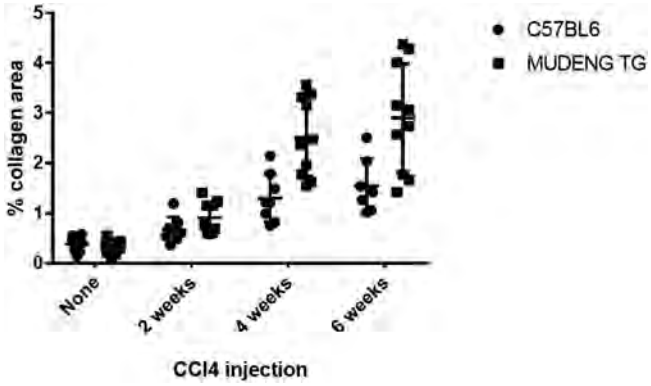

Figure 1: The collagen proportionate area between the MUDENG and C57BL/6N mice is significantly different starting at week 2 after intraperitoneal injection of CCl_4.

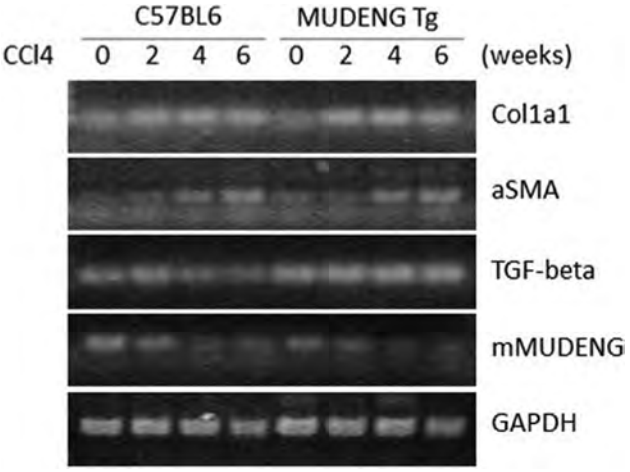

Fig 2. Greater expression of TGF-β throughout the life span in MUDENG transgenic mice compared to C57BL/6N was noticed.

Conclusion: MUDENG transgenic mice demonstrates rapid development of fibrosis compared to C57BL/6N mice. Further studies to evaluate the pathways altered by MUDENG overexpression inducing accelerated liver fibrosis should be done.

FRI232

Thrombofibrosis: inherited thrombophilia as a cause of significant liver fibrosis

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Background and Aims: inherited hypercoagulable states can favor the progression of hepatic fibrogenesis in patients with chronic liver

disease of different etiologies and lead to vascular diseases of the liver. Moreover, it has been recently suggested that they are *per se* a cause of significant liver fibrosis. Our aim was to determine the prevalence of significant/advanced fibrosis and hepatic vascular disease in a cohort of patients with inherited thrombophilia.

Method: we performed a unicenter, cross-sectional study. Patients with inherited thrombophilia diagnosed by the Hematology Department between May 2013 and February 2017 were included. A complete laboratory analysis for liver disease, FibroScan® and abdominal ultrasound were performed. The FibroScan® threshold to consider fibrosis as significant was >8 Kpa. In those patients with suspected liver disease, a liver biopsy and/or computed tomography/magnetic resonance imaging were additionally performed according to clinical criteria.

Results: 241 patients with inherited thrombophilia (25.7% had combined thrombophilia) were included. The mean age was 46.2 ± 14.3 years, 61.4% were women and 99.6% Caucasian. The most frequent disorders were Factor V Leiden (36.1%) and Factor II Mutation (35.7%). Thrombotic complications and/or abortion had been experienced by 53.5% of patients. Anticoagulant and antiplatelet therapy had been prescribed in 27.8% (median time (IQR): 11.1 (5.1–35.9) months) and 25,3% (28.8 (13.5–47.9) months) of patients, respectively. Risk factors for liver disease were present in 54.8% of patients, the most important being dyslipidemia (27.4%), obesity (24.9%) and excessive alcohol consumption (10.4%). Eight patients (3.3%) had significant fibrosis, of whom 2 (0.8%) were cirrhotic. These 8 patients had at least one risk factor for liver disease. The only variables associated with the presence of significant fibrosis were a more advanced age (54.5 vs. 45.9 years, $p < 0.001$) and the presence of risk factors for liver disease (100 vs. 53.2%, $p = 0.009$). Regarding vascular disorders of the liver, nine patients (3.7%) had or had had a portal vein thrombosis, without diagnosing any case of Budd-Chiari syndrome or portosinusoidal vascular disease. No variable was associated with the development of non-cirrhotic portal vein thrombosis.

Conclusion: all patients with significant and/or advanced liver fibrosis had risk factors for liver disease and were older. These data do not support inherited thrombophilia as a cause of liver disease. The prevalence of vascular diseases of the liver was low and was not associated with any variable.

FRI234

An improved method for liver fibrosis assessment using magnetic resonance elastography

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Background and Aims: Liver stiffness measurement (LSM) allows indirect measurement of liver fibrosis. Transient elastography (TE) is often selected over magnetic resonance elastography (MRE) due to costs and logistics. However, TE has similar limitations to liver biopsy in accuracy of assessment of general liver stiffness (LS) as each method only measures 1:500 and 1:50000 respectively of the whole liver volume. Hence, the current approach is suboptimal in ruling out significant fibrosis.

Method: This is a retrospective analysis on MRE images of 171 subjects at our hospital between April 2017- March 2019. Four planes of MRE images were selected as per standard protocol and region of interests (ROI) were drawn to measure LS. Blood vessels, bile ducts and areas near to the heart were excluded. Each plane consisted of ROIs selected at 12 different points within the right liver lobe which were arranged into outer, middle and inner bands (4 points within each band). Generalized measurements were also made of the 3 bands. We compared the differences of LS across different bands horizontally and vertically. The differences in LS between the bands and the mean of the 4 points in each corresponding band were also compared.

Results: The most common conditions were non-alcoholic fatty liver disease/steatohepatitis (48%) and chronic hepatitis B (20%). Patient demography was – Age (59 +/– 13), Chinese (83%, N = 141) and Male (64%, N = 109). There was significant difference in LSM between bands of each plane ($p < 0.01$) and vertically especially in the outer region of the right liver lobe.

Table: Differences between measured bands

Plane	Measured Mean		Difference (95% CI)	*p* value
	Band (1–4)	Band (9–12)		
A, Median (IQR)	3.46 (1.85)	2.81 (1.62)		**<0.001**[b]
B, Mean (SD)	3.95 (1.70)	3.39 (1.62)	0.56 (0.46, 0.66)	**<0.001**[a]
C, Mean (SD)	3.84 (1.65)	3.22 (1.43)	0.61 (0.51, 0.72)	**<0.001**[a]
D, Mean (SD)	3.83 (1.70)	3.26 (1.43)	0.58 (0.45, 0.71)	**<0.001**[a]

[a]Paired sample t test;
[b]Wilcoxon signed rank test

Conclusion: Systematic analysis of MRE images demonstrates differences in LS within the right liver lobe both vertically and horizontally. Perhaps TE should not be used as a precise method to exclude significant LS as it only measures the outer 3 cm^3 of the liver. This would underestimate the prevalence of advanced LS. Also, vertical differences of LS could explain TE report variability when LSMs are performed across different liver locations during the same assessment period.

FRI235

Expression of cyclin E1 and CDK2 in hepatic stellate cells is critical for initiation and progression of liver fibrosis in mice

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Background and Aims: Liver fibrogenesis is a wound healing process characterized by the accumulation of extracellular collagen produced by Hepatic Stellate Cells (HSCs). Initiation of liver fibrosis involves cell cycle re-entry and thus activation and proliferation of normally quiescent HSCs. It is believed that the cyclin-dependent kinase 2 (Cdk2) together with its regulatory subunit Cyclin E in general controls cell cycle re-entry. We have recently shown that constitutive ablation of Cyclin E1 (CcnE1) in mice inhibited liver fibrogenesis. However, the effector cells of CcnE1 during fibrogenesis are not known so far and it has also not been clarified yet, whether the pro-fibrotic effect of CcnE1 depends on the kinase activity of Cdk2. Thus the aim of the present study was to evaluate the contribution of CcnE1 and Cdk2 specifically in HSCs for liver fibrogenesis.

Methods: We generated HSC-specific knockout mice for CcnE1 ($CcnE1^{\Delta HSC}$) and Cdk2 ($Cdk2^{\Delta HSC}$) by crossing floxed (*i.e.* $CcnE1^{f/f}$/$Cdk2^{f/f}$) mice with transgenic mice expressing cre-recombinase under the control of the L-rat promoter. Liver fibrosis was induced by treating mice with a combination of Diethylnitrosamin (DEN) and CCl_4 or with CCl_4 only according to established protocols. For

pharmacological inhibition of Cdk2 kinase activity the pan-Cdk inhibitor CR8 was applied *in vitro* on HSC cell lines (LX-2, human; GRX, murine) and in primary murine HSCs.
Results: Genetic ablation of Cdk2 specifically in HSCs significantly reduced collagen accumulation and fiber formation in the liver after CCl_4 treatment when compared to cre-negative littermates. Accordingly, $Cdk2^{\Delta HSC}$ mice showed a significantly reduced HSC activation in the liver. Similarly, $CcnE1^{\Delta HSC}$ mice revealed significantly reduced liver fibrosis in comparison to cre-negative littermates after DEN/CCl_4 treatment, which was however not associated with a reduced liver cancer incidence as initially hypothesized. In good agreement with these findings, treatment with CR8 inhibited kinase activity, proliferation, survival and pro-fibrotic activation of HSCs (*i.e.* primary cells and cell lines) *in vitro.*
Conclusion: The pro-fibrotic properties of HSCs depend on functional Cdk2 and CcnE1. This suggests that cell cycle re-activation of naïve HSCs *in vivo* requires functional CcnE1/Cdk2 kinase activity. We conclude that pharmacological inhibition of Cdk2 kinase activity in HSC could be an alternative approach to treat liver fibrosis.

FRI236

Non-canonical autophagy in myeloid cells constrains hepatic and systemic inflammation and limits fibrosis

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Background and Aims: Sustained hepatic and systemic inflammation, in particular originating from monocytes/macrophages, is a driving force for chronic liver disease progression to cirrhosis. Therefore, reprogramming monocyte/macrophage phenotype has emerged as a strategy to limit inflammation during chronic liver injury. LC3-associated phagocytosis (LAP) is a non-canonical form of autophagy that shifts monocyte/macrophage phenotype to an anti-inflammatory phenotype. This phagocytic process results in the recruitment of some, but not all, members of the autophagic machinery and is functionally and mechanistically distinct from the canonical macroautophagic process. Here, we investigated whether LAP is involved in the regulation of inflammation and fibrosis.
Method: LAPosome number were quantified in blood and liver monocytes from patients with cirrhosis and control subjects following incubation with either pHrodo^{TM} red *E. coli* Bioparticles or IgG latex beads and immunostained with an anti LC3 antibody. FcγRIIA expression and inflammatory profile were evaluated in human monocytes from patients with cirrhosis and healthy donors by flow cytometry. LysMCre $Rubicon^{flox/flox}$ mice (LAP-deficient in myeloid cells), human $FcγRIIA^{Tg}$ mice expressing the human $FcγRIIA^{R131}$ isoform and WT littermates were exposed to chronic carbon tetrachloride (CCl_4) administration or subjected to bile duct ligation (BDL).
Results: Recruitment of LC3 to pHrodo+phagosomes (LAPosomes) was minimal in blood and liver monocytes from healthy donors, and enhanced in cells from patients with cirrhosis, and in mice exposed to chronic administration of CCl_4 or BDL. Pharmacological inhibition of LAP components exacerbated the inflammatory signature in monocytes from patients with cirrhosis. Similarly, LysMCre $Rubicon^{flox/flox}$ mice showed enhanced hepatic inflammatory profile upon chronic exposure to CCl_4 or following BDL, resulting in enhanced liver fibrosis. Mechanistically, cirrhotic patients show increased monocyte expression of FcγRIIA and enhanced engulfment of monomeric IgG in LC3+ phagosomes. In keeping, mice overexpressing human FcγRIIA in myeloid cells show enhanced LAP in response to chronic liver injury, and were resistant to inflammation and liver fibrosis.
Conclusion: These data shed light on a novel role for LC3-associated phagocytosis as an anti-inflammatory pathway in monocytes that constrains both systemic and hepatic inflammation during cirrhosis, with potent antifibrogenic effects driven by monomeric IgG-FcγRIIA.

FRI237

Reduction in types I and III collagen gene expression by an alphavbeta1 integrin inhibitor correlates with a decrease in PRO-C1 and PRO-C3 levels in precision-cut liver tissue slices from cirrhotic non-alcoholic steatohepatitis patients

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Background and Aims: The interactions of multiple cell types with the extracellular matrix involved in fibrogenesis is difficult to reproduce in cell cultures, thus translation of antifibrotics to clinical settings remains a challenge. Types I and III collagen are the most prominent fibrillar collagens of the fibrotic matrix produced by fibroblasts. Type III collagen formation, measured by the PRO-C3 neoepitope marker, has been shown to be useful for prognostic, diagnostic, and therapeutic assessment in liver diseases in humans. Integrin $\alpha_V\beta_1$ is a (myo)fibroblast-specific integrin that activates transforming growth factor (TGF)-β, promoting fibrogenesis. Inhibition of $\alpha_V\beta_1$ is antifibrotic in mouse models; however, data in human tissue are limited. The study aims were to use human precision-cut liver tissue slices (PCLivS) to 1) assess fibrogenesis through measurement of types I and III collagen gene expression and pro-peptides released into culture media and 2) evaluate the antifibrotic efficacy of $\alpha_V\beta_1$ inhibition.
Method: PCLivS were obtained from cirrhotic nonalcoholic steatohepatitis (NASH) patient tissue explants and cultured in the presence of a small-molecule, selective, $\alpha_V\beta_1$ inhibitor or a TGF-β receptor kinase (ALK5) inhibitor. After 2 days, tissue was harvested for gene expression analysis and culture medium for biomarker analysis. Gene expression was assessed using the NanoString platform, and biomarkers of types I (PRO-C1) and III (PRO-C3) collagen formation were assessed by enzyme-linked immunosorbent assay (ELISA; Nordic Bioscience).
Results: Treatment of PCLivS from NASH patients with an $\alpha_V\beta_1$ or ALK5 inhibitor reduced expression of pro-fibrogenic genes. *COL1A1* and *COL3A1* gene expression was reduced as was release of PRO-C1 and PRO-C3. There was a significant correlation between relative *COL1A1* and *COL3A1* gene expression and relative PRO-C1 and PRO-C3 biomarker levels.
Conclusion: Using PCLivS from cirrhotic NASH patient livers, a strong correlation was observed between types I and III collagen gene expression and their respective biomarker levels, both were reduced in response to antifibrotic treatment via $\alpha_V\beta_1$ integrin or ALK5 inhibition. Thus, these data confirm the validity of PRO-C1 and PRO-C3 as biomarkers of fibroblast collagen gene expression and, therefore, as suitable translational markers of fibrogenesis in PCLivS assays. Furthermore, the data support the evaluation of an $\alpha_V\beta_1$

integrin inhibitor for the treatment of advanced liver fibrosis associated with NASH.

FRI238

Active role of sphingosine-1-phosphate in promoting peripheral-dominant liver fibrosis in mice model of congestive hepatopathy

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Background and Aims: Congestive hepatopathy (CH) is an entity of non-viral chronic liver disease that often develops to liver fibrosis and liver cancer. As a prototype of CH, Fontan-associated liver disease (FALD) has been increasing in adults due to longer survival after Fontan procedure. Recently, European cohort study on FALD showed that majority of hepatic nodules were found in peripheral part of the liver, suggesting the close link between peripheral dominance of fibrosis and carcinogenesis. However, the underlying molecular mechanisms of liver fibrosis by CH remain largely undisclosed. Sphingosine-1-phosphate (S1P), mainly synthesized by sphingosine kinase 1 (SphK1), is one of lipid mediators in cellular proliferation or differentiation, thus involving in fibrosis or carcinogenesis. In this study, we sought to clarify the mechanisms of congestion-induced liver fibrosis, by focusing on the impact of S1P on regional fibrosis distribution.
Method: Congestive hepatic fibrosis was induced by partial ligation (0.6 mm) of the suprahepatic inferior vena cava (pIVCL) of C57BL/6J male mice (aged 8–12 weeks). After 6 weeks of the operation, liver fibrosis was evaluated by Sirius red staining and αSMA staining. To assess fibrosis distribution, we performed such quantification in both central (around large vessels) and peripheral (near liver surface) part of the liver. Liver S1P was quantified by liquid chromatography mass spectrometry. The expressions of fibrosis-related and S1P-related genes were evaluated by laser microdissection. To clarify the involvement of S1P in fibrosis, we treated pIVCL mice with antagonists for S1P receptor (S1PR) 1 (Ex26), S1PR2 (JTE013), or S1PR3 (CAY10444), respectively.
Results: After 6 weeks of pIVCL, congestive hepatic fibrosis were significantly induced in the peripheral rather than central part of the liver. Such regional disparities in fibrosis were not observed in other liver fibrosis models (CDD-induced NASH-like model/ CCl4-induced fibrosis model). Vascular extravasation, as a consequence of congestion, was mainly appeared in the peripheral part and tended to colocalize with fibrosis distribution. Liver S1P levels in the pIVCL mice were significantly elevated compared to the control. The expressions of SphK1 and fibrosis related genes were significantly elevated in the peripheral part than that in the central part of the liver. Blockade of S1P/S1PR2 axis by JTE013 alleviated fibrosis in the pIVCL mice, while blockade of S1PR1 and S1PR3 failed to do so.
Conclusion: In mice model of congestive hepatopathy, liver fibrosis accompanied by extravasation is more prominent in the peripheral part of the liver. The activation of SphK1-S1P-S1PR2 axis in this model supports for a possibility that, S1P pathway serves as a therapeutic target for the congestion-induced, peripheral-dominant liver fibrosis, such as FALD.

FRI239

CRV431 decreases diet- and chemical-driven fibrosis in livers of mice

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Background and Aims: Liver fibrosis is the prevalent pathological feature of chronic hepatic injuries. With limited treatment options available for fibrotic patients, identification of novel, effective antifibrotic compounds is crucial. We previously reported that CRV431, a potent pan-cyclophilin inhibitor, decreased collagen deposition in mice administered carbon tetrachloride (CCl_4). Moreover, similar results were observed in mice under high fat diet. Here, we examined whether CRV431 decreases diet- and chemical-induced fibrosis in mice.
Method: Male C57BL/6J mice were nourished with the Western diet that includes chow containing 21.1% fat, 41% sucrose, and 1.25% cholesterol by weight and high sugar solution (23.1 g/L fructose and 18.9 g/L glucose). 0.2 uL/g CCl_4 were administered intraperitoneally once weekly. After 6 weeks, mice (n = 8 to 10 per group) were randomly assigned to receive daily oral gavage with 50 mg/kg CRV431, 10 mg/kg obeticholic acid (OCA, a comparator), combination (COMBO) of CRV431 and OCA, or vehicle for 6 weeks until sacrifice. Negative control mice were included. Body weight and liver weight were recorded. Livers were histologically examined for inflammation, steatosis, and ballooned cells. Collagen was measured by Sirius Red staining of hepatic tissues. Glucose, cholesterol, alanine transaminase (ALT), aspartate transaminase (AST), and alpha fetoprotein (AFP) levels were detected from sera. Two-tailed Bonferroni's multiple comparison statistical analyses, with alpha value set at 0.05, were conducted with GraphPad Prism.
Results: A 65% reduction in hepatic collagen deposition was observed in CRV431 treated mice compared to control animals ($p < 0.0001$). OCA-treated animals demonstrated a 39% reduction in collagen deposition. The COMBO group demonstrated a 67% reduction in collagen deposition. This was not statistically different from CRV431 alone or from negative control with stained collagen. CRV431 and COMBO also lowered body weight compared to vehicle ($p = 0.0129$ and 0.0055, respectively), which was not observed with OCA alone. Glucose, AST, ALT, cholesterol, inflammation, steatosis, and ballooning were unaffected by treatment ($p > 0.05$).
Conclusion: CRV431 is a potent agent against diet- and chemical-driven fibrosis. This result is consistent with our previous findings and suggests that cyclophilin inhibition can protect the liver from induced injuries.

FRI240

Fibrosis progression in NASH: real- world data from the US population

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Background and Aims: GAIN is a retrospective and cross-sectional study in which a sample of secondary care physicians (hepatologists, gastroenterologists, endocrinologists and diabetologists) recruited from public and private hospitals and practices provided clinical and resource use information on patients with NASH diagnosis via an online survey.
The aim of this analysis was to study fibrosis progression between clinical diagnosis and date of follow-up for the US patients (n = 1,221).
Method: Descriptive analysis of US patients' characteristics and of the fibrosis progression for patients. Chi squared and odds-ratios were used to test differences in proportions.
Results: Out of 1,221 patients recruited in USA, 52% were male, mean age was 50.9 (10.9), BMI 31.8 (13.2) and most frequent comorbidities were obesity (36.6%) Diabetes (21.1%); Dyslipidaemia (27.4%) and Hypertension (24.8%). Additionally, 3.1% had cardiovascular diseases (CV, including infarction, heart failure and angina). 554 had at least 1 drug prescribed for NASH at the time of the diagnosis. For those who had a NASH treatment, 33.6% were on Statins, 31.8% on Vitamin E, 30% were on Metformin, 12.5% on Omega-3 fatty acids, 9.2% on

Thiazolidinediones, 6.1% on other anti-diabetic medication and 27% other medications.
1,016 patients had measurements of fibrosis stage at both diagnosis and at follow-up, therefore fibrosis progression could only be evaluated for those individuals. Additionally, fibrosis evaluation was performed with biopsy for 54.8% of patients at diagnosis and 30.4% at follow up date, while non-invasive blood tests and imaging techniques where used when biopsy wasn't performed. At diagnosis, 201 (20%) were F0, 293 (29%) F1, 233 (23%) F2, 136 (13%) F3, 126 (12%) F4 Compensated cirrhosis and 27 (3%) F4 Decompensated cirrhosis.
Amongst patients who progressed to next stage or advanced stage (141 patients), 59% had obesity, 57% had either Hypertension, Dyslipidaemia, T2D or cardiovascular diseases. Amongst those who regressed (84 patients) to previous stage or were stable (791 patients), 42% had obesity, 55% had either Hypertension, Dyslipidaemia, T2D or cardiovascular diseases (p = 0.006).
Likelihood of progression is 1.75 times more than regression. Chance of progressing were higher for patients with Obesity (Odds ratio (95% CI) = 2.003 (1.158–3.467)) and CV.
Conclusion: Progression of fibrosis stage in NASH was more likely among obese. Further analysis is granted to understand the role of treatment on disease progression.

FRI241

Nanoparticular bisphosphonate induces an anti-fibrotic response by modulation of fibrosis associated genes and pathways in (non-) parenchymal liver cells in CCl4 fibrotic mice

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Background and Aims: Bisphosphonates, e.g. Alendronate (AL), inhibit osteoclasts, a specialized population of macrophages. AL showed an anti-fibrotic together with an anti-tumor effect via macrophage (re-)polarization in rat hepatocellular carcinoma [Rogers T et. al., J. Transl. Med. 2011]. However, after intravenous application, bisphosphonates are sequestered in bone and rapidly excreted by the kidneys. Therefore, we aimed to develop nontoxic nanohydrogel particles (NHP) with covalently linked Alendronate (AL-NHP) that primarily home to the liver.
Method and Results: Stable AL-NHP with diameters below 100 nm were synthesized by controlled-radical polymerization. In primary murine macrophages, AL-NHP induced no cytotoxic effect compared to free AL (up to 60 µM AL). AL-NHP (30 µM AL) repolarized M2-type macrophages towards anti-fibrotic and anti-tumorous M1-type macrophages, increasing macrophage expression of TNF-a and Interferon-g, as determined on the transcript and protein level via qPCR and FACS analysis. After intravenous (iv) injection in both healthy and CCl_4 liver-fibrotic Balb/c mice, more than 80% of near-infrared fluorescence labeled CS800-AL-NHP rapidly accumulated in the liver, whereas CS800 labeled AL was readily cleared via the kidneys. On the cellular level, CS800-AL-NHP were effectively taken up by liver macrophages (>90%), hepatocytes (>90%) and portal myofibroblasts (>90%) as determined by FACS. CS800-AL-NHP were well tolerated and showed no toxicity. Mice gavaged with escalating doses of CCl_4 over 5 weeks, were treated with iv AL-NHP (1.2 or 2.4 mg/kg AL) thrice weekly from week 4–5, while fibrotic controls received equal concentrations of AL or empty NHP. On sacrifice, liver collagen and alpha-SMA expressing myofibroblasts were significantly reduced to non-fibrotic control levels in AL-NHP treated vs. control mice, as determined by hepatic Sirius Red stained collagen and hydroxyproline content, while free AL and empty NHP were ineffective. Staining for alpha-SMA, and RNA-NGS-sequencing of livers from AL-NHP (2.4 mg/kg) revealed a significant downregulation of numerous fibrosis-related genes, and profibrotic pathways in both macrophages and myofibroblasts/hepatic stellate cells.
Conclusion: We have designed an AL-NHP as a biocompatible nanocarrier for the bisphosphonate Alendronate. In contrast to soluble AL, AL-NHP was almost exclusively sequestered by the liver, and efficiently taken up in all non-macrophages and activated myofibroblasts/hepatic stellate cells. In CCl_4 fibrotic mice, late-onset treatment with AL-NHP reduced liver collagen down to normal levels by beneficial of a broad range of fibrosis-relevant genes and pathways.

FRI242

Microscopy-based fibrosis phenotypic analysis of animal and human NASH cohorts reveal translational traits of fibrosis progression and severity

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Background and Aims: To date, no single rodent model can display the whole disease spectrum and metabolic features associated with human NASH but can only imitate characteristics. In this study, we focus on the phenotypic traits of fibrosis severity from three rodent fibrosis progression models and an adult human NASH progression cohort. In each model and for each progression stage, we quantify 31 different traits (145 parameters) of the fibrosis phenotypes. We identified the traits of fibrosis severity that are common to all the species.
Method: The rodent models include (1) a Bile Duct Ligation (BDL) fibrosis progression cohort (Sham, Day 5, 10, 14 and 20) (N = 5/grp), (2) a thioacetamide (TAA) induced fibrosis (ctrl, week 4 and 8 (N = 5/grp), and (3) a methionine and choline-deficient (MCD) fat diet (ctrl, week 8 and 12) (n = 4–10/grp). The clinical cohort is comprised of patients with NASH diagnosed by histologic assessment of liver biopsy according to NASH CRN criteria by pathologists (N = 98, F0(24), F1(24), F2(25), F3(20) and F4(5)). Unstained tissue slides were imaged at 20× with a Genesis200® Two- Photon microscopy system. FibroNest©, a novel cloud-based fibrosis image analysis platform, is used to quantify fibrosis phenotypes for the collagen content and structure (12 traits), the morphometric traits (12) of the collagen fibers, and fibrosis texture traits (7). Each trait is described by parameters (qFPs) to account for the mean, variance, and progression. AVenn Diagram is used to summarize the fibrosis progression (PqFP) that are common between animal and human models.
Results: Most of the PqFp identified for the TAA model are texture-based and only the Count of Tortuous fibers was translated to the other rodent models, but not to the NASH human model. The BDL model exhibited 6 PqFPs in common with the NASH model, but only 4 with the MCD model. The MCD model exhibited 3 PqFP in common with the NASH human model, including collagen area, density, and skeleton nodes.
Conclusion: We identified 3 significant fibrosis traits out of 31 that are translational to the BLD, MCD, and Adult NASH phenotypic models: Collagen Area Ratio, Collagen Fiber Density, and the qFPs

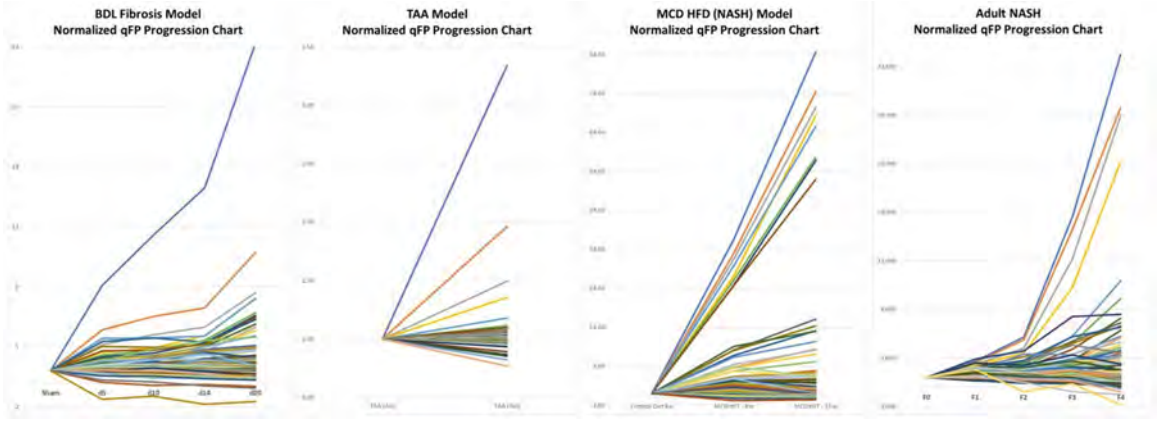

Figure: (abstract: FRI242)

associated with the skeleton of the collagen fibers (Skeleton Length, Skeleton nodes density). This result confirms that the phenotype of fibrosis in each model is fundamentally different. It also has the potential to improve the quality of translational drug discovery and development process and to yield specific biopsy-based diagnostic tools for fibrosis.

FRI243

Fibrosis phenotypic analysis of collagen stained liver histology sections discern anti-fibrotic agents in DDC- induced cholangitis mouse model

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Background and Aims: Primary sclerosing cholangitis (PSC) is a chronic liver disease caused by progressive inflammation, fibrosis, and strictures of hepatic bile ducts, often leading to biliary cirrhosis. Transforming growth factor beta (TGF-b) and its activation by alpha v beta 6 (avb6) integrin are key players in the pathogenesis and exacerbation of fibrosis. Here, we assess the anti-fibrotic efficacy of SB30 (TGF-b receptor I (ALK5) inhibitor) and 3G9 (anti-avb6) in a chemically induced cholangitis mouse model with a focus on the phenotypic quantification of fibrosis.
Method: Mice (8 wks old, n = 8–10/grp) were fed with 0.1% DDC (3,5 diethoxycarbonyl- 1,4-dihydrocollidine)-diet for 20 days to induce biliary fibrosis and cholestasis. A small molecule ALK5 inhibitor, SB30) (30 mpk, PO, bid), and a blocking antibody against mouse avb6, 3G9 (10 mpk, IP injection, bid) were administered in DDC mice starting at diet initiation. Liver histology sections stained with Picro-Sirius Red were imaged with light microscopy. We developed a novel cloud-based image analysis platform to quantify fibrosis for the collagen content and structure, morphometric trait of each individual collagen fibers, and the fiber texture (relative arrangement of the fibers). Each morphometric and texture trait is described by several quantitative fibrosis parameters (qFPs) to account for mean, variance, and progression. qFPs were combined to generate a Composite Fibrosis Score (CFS), a continuous phenotypic quantifier of fibrosis.
Results: SB30 reduced liver collagen fiber area and fiber network structures (80% and 50%, respectively, compared to DDC-Vehicle), while 3G9 decreased it to a lesser degree (10% and 15%, respectively). The qFPs, reported on heat charts, show highest values for DDC-Vehicle, mid values for SG9, and lowest values for SB30. SB30 is more effective than 3G9 in improving fibrosis area and structure index, qFPs, and Composite Fibrosis Scores (SB30 40% and 3G9 20% reduction compared to DDC- Vehicle).
Conclusion: SB30 has higher anti-fibrotic effects compared to 3G9 in chronic DDC-induced PSC model for improving liver histopathology. These data show that phenotypic fibrosis analysis of collagen from stained histological images is an effective method to describe and quantify the severity and progression of liver fibrosis and may differentiate pharmacological agents.

FRI244

Dietary wheat amylase trypsin inhibitors activate myeloid cell toll-like receptor 4 to enhance chronic liver disease in murine liver fibrosis and hepatocellular carcinoma

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Background and Aims: Specific bioactive nutritional components affect the intestinal immune system. The gut-liver axis is increasingly recognized as a central modulator of liver health and disease. We hypothesized that nutritional wheat amylase trypsin inhibitors, compact molecules that resist intestinal proteolysis and that activate intestinal myeloid cells via toll-like receptor 4 (TLR4), may promote murine liver fibrosis and hepatocellular carcinoma (HCC).
Method: The following murine models for liver fibrosis and HCC, respectively, were employed: 1) Male *Mdr2*(Abcb4)–/– mice that develop spontaneous biliary fibrosis resembling human PSC; 2) male *Mdr2*–/– mice were injected intraperitoneally with a single dose of diethyl-nitrosamine (DEN, 10 μg/g of bw at age 5 days old), followed by 0.05% phenobarbital in drinking water starting at the 3 weeks of age. Mice received a well-defined, wheat free and zein (non-inflammatory protein from corn) containing diet with or without 1.5% of the protein being replaced by ATI from age 4–10 weeks (fibrosis model), or from age 1–5 months (HCC model).
Results: 1) *Mdr2*–/– mice fed the ATI-containing diet developed significantly increased hepatic fibrosis (Sirius red staining and hydroxyproline content) and serum transaminases vs the ATI-free controls. Gene expression analysis (*il1b*, *tnfa*, *cd68*, *col1a1*, *asma*, *col3a1*, *mmp13*, *timp1* and *mmp9),* quantitative immunohistochemistry (CD68+macrophages, alpha-SMA+ myofibroblasts and CK19+ cholangiocytes), and FACS analysis (infiltrating inflammatory monocytes-macrophages) confirmed a significantly increased inflammation, ductular proliferation and fibrogenesis in the ATI-fed vs the control mice. 2) ATI feeding of the HCC bearing mice significantly increased tumour burden, and induced higher transcript levels of *vefg, hif1a, mmp9, arg1* compared to mice on the control diet. ATI-fed mice showed significantly increased numbers of hepatic M2-type macrophages ($CD11b^{high}$ $CD206^{high}$), myeloid derived suppressor cells ($Ly6c^{high}$, $Ly6G^{-}CD11b^{+}$), and $CD4^{+}$ Treg cells vs the ATI-free HCC

bearing mice. Furthermore, their numbers of Glypican-3, Ki67, CD68, and Ym-1 positive cells were significantly increased in parallel with the accelerated tumor growth, proliferation and tumor associated immune suppression.
Conclusion: Ingestion of dietary wheat ATI in amounts comparable to average daily human intake promote murine liver fibrosis and primary liver cancer.

FRI245
Epigenetic mechanism and metabolic reprogramming in fibrogenesis: dual targeting of G9a and DNA methyltransferase 1 for the inhibition of liver fibrosis

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Background and Aims: Hepatic stellate cells (HSC) transdifferentiation into myofibroblasts is central to fibrogenesis. Epigenetic mechanisms, including histone and DNA methylation, play a key role in this process. Concerted action between histone and DNA-mehyltransferase like G9a and DNMT1 is a common theme in gene expression regulation. We aimed to study the efficacy of CM272, a first-in-class dual and reversible G9a/DNMT1 inhibitor, in halting fibrogenesis.
Method: G9a and DNMT1 were analyzed in cirrhotic human livers, mouse models of liver fibrosis and cultured mouse HSC. G9a and DNMT1 expression was knocked-down or inhibited with CM272 in human HSC (hHSC), and transcriptomic responses to transforming growth factor-β (TGFβ) and hypoxia were examined. Glycolytic metabolism and mitochondrial function were analyzed with Seahorse-XF technology. Gene expression regulation was analyzed by chromatin immunoprecipitation and methylation-specific PCR. Antifibrogenic activity and safety of CM272 were studied in mouse chronic CCl_4 administration and bile duct ligation (BDL), and in human precision-cut liver slices (PCLSs) in a new bioreactor technology.
Results: G9a and DNMT1 were detected in stromal cells in areas of active fibrosis in human and mouse livers. G9a and DNMT1 expression was induced during mouse HSC activation, and TGFβ triggered their chromatin recruitment in hHSC. G9a/DNMT1 knockdown and CM272 inhibited TGFβ fibrogenic responses and hypoxia adaptation in hHSC. TGFβ-mediated profibrogenic metabolic reprogramming was abrogated by CM272, which restored gluconeogenic gene expression and mitochondrial function through on-target epigenetic effects. CM272 inhibited fibrogenesis in mice and PCLSs without toxicity.
Conclusion: Dual G9a/DNMT1 inhibition by compounds like CM272 may be a novel therapeutic strategy for treating liver fibrosis.

FRI246
FIB-4 and APRI scores re-validation; a cohort study of 69106 chronic hepatitis C patients

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Background and Aims: FIB-4 and APRI are simple, non-invasive, inexpensive scores however, its accuracy is questioned. The Egyptian National Committee for Control of Viral Hepatitis has provided a rich pool of electronic patients' records with liver biopsy results. So, we were motivated to have the chance to revise and validate the accuracy of FIB-4 and APRI scores, and to go further step to explore the potentials of developing an accurate prediction method using machine learning approach.
Method: This retrospective multi-center study included 69106 Egyptian patients with HCV for interferon-based antiviral therapy from 2010–2014 where liver biopsy was mandatory for fibrosis assessment. FIB-4 and APRI scores were calculated and its performance analysis was assessed versus to Metavir scoring system (F0-F4) as a gold standard of liver fibrosis. Machine learning (ML) was used for feature selection and reduction to the most relevant attributes (CfsSubseteval / best first).
Results: In this study, 57492 (83.2%) patients had F0- F2, and 11615 (16.8%) patients had F3-F4. Any score validation involves the evaluation of discrimination represented by AUC, and calibration to assess agreement between predicted and observed risks (correctly classified). The revalidation of FIB-4 and APRI showed low accuracy and high disagreement with biopsy results, with overall AUC 0.68 and 0.58 respectively (Table 1). FIB-4 diagnoses few cases (14%) of F3-F4 patients, the high specificity, and negative predictive values of FIB-4 and APRI just reflect the low prevalence of F3-F4 in the study population. The high disagreement between APRI, FIB-4 and biopsy provided the motivation to develop our ML approach. Out of 15 attributes machine learning has selected Age (>35 years), AFP (>6.5), and platelet (<150,000) as the most relevant risk attributes at these cut off values. Any patient with one or more of these risk factors will be considered as a possible F3-F4 with a classification accuracy up to 92% and ROC Area 0.74 (Table 1). This high sensitivity will ensure that high risk F3-F4 patients will not be missed to be assessed appropriately and to minimize fibrosis screening by 40% which is the percent of patients with no risk factors.

	FIB4 ≥ 1.45	FIB4 ≥ 3.25	APRI ≥ 1	ML approach
Sensitivity	57.5%	13.9%	32.7%	92%
Specificity	68.5%	96.5%	80.68%	49%
PPV	27.6%	45.2%	25.1%	34%
NPV	88.5%	84.3%	85.8%	95.5%
Disagreement with Metavir score	42.5%	86%	67%	8%
ROC area		0.69	0.58	0.74

Conclusion: This revalidation study showed that the two popular FIB-4 and APRI scores are not accurate, and miss the diagnosis of most of F3-F4 patients. ML implementation helps the empowerment of medical decision and minimizes the dimensionality of clinical data to three risk factors (Age, AFP and Platelet). This approach does not need any calculation and provides an accurate F3-F4 diagnosis superior to APRI, FIB-4 scores.

FRI247

Integrin alphaVbeta1 inhibition ameliorates liver fibrosis in mice

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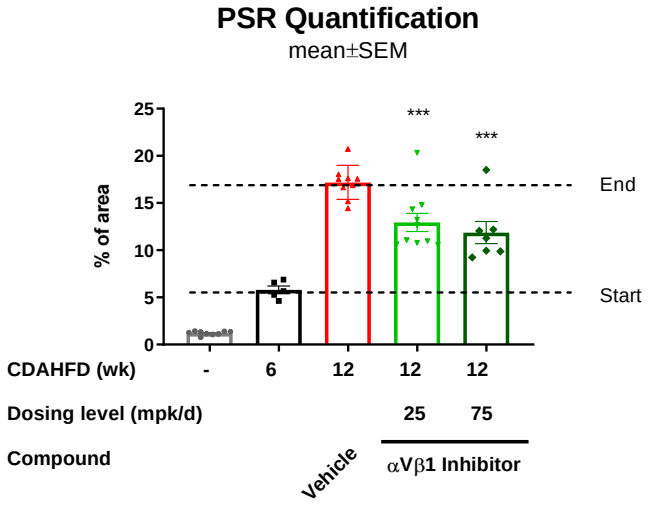
Background and Aims: Integrins are heterodimeric membrane proteins composed of alpha and beta subunits that regulate cellular activity by integrating the extracellular and intracellular environments in a bidirectional manner. Integrin alphaVbeta1, found highly expressed in activated fibroblasts, has been implicated in fibrogenesis, by binding to latency-associated peptide (LAP) of pro-transforming growth factor beta (TGF-beta) to liberate active TGF-beta. However, given alphaVbeta1′s low affinity towards LAP, its exact mechanism of action in rodent fibrosis models and human translational systems remains to be fully elucidated.
Method: Integrin alphaVbeta1 heterodimer expression was determined by co-immunoprecipitation of the alphaV and the beta1 subunits. Activation of TGF-beta was determined by the luciferase activity in TGF-beta reporter cells, co-cultured with Chinese Hamster Ovary (CHO) cells over-expressing human alphaVbeta1 and pro-TGF-beta1. Active and total TGF-beta in conditioned media from LX-2 cells and primary human hepatic stellate cells (HSC) were measured by an enzyme-linked immunosorbent assay (ELISA). HSC migration was measured by Incucyte migration module. An orally bioavailable, selective small molecule alphaVbeta1 antagonist was identified. The in vivo effects of the molecule were examined in the choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD)-induced mouse nonalcoholic steatohepatitis (NASH) model.



***p<0.001 vs vehicle by One Way Anova and Dunnett's multiple comparisons

Results: While alphaVbeta1 modestly mediated TGF-beta activation in an engineered cell line, no appreciable level of TGF-beta activation by this integrin was detected in cultured HSC cell line and primary human HSCs. This is consistent with 100× lower affinity between alphaVbeta1 and LAP, compared to that between alphaVbeta6 and LAP. Nonetheless, we observed significantly attenuated HSC migration in vitro and dampened fibrosis in a CDAHFD-induced NASH model by alphaVbeta1 blockade. Deep sequencing analyses suggest that alphaVbeta1 blockade may regulate anti-oxidation, fibrolysis, and inflammatory pathways in CDAHFD mouse liver. Moreover, alphaVbeta1 inhibition modulated common gene signatures that are elevated in both mouse liver fibrosis and human NASH with advanced fibrosis stage (F3/F4). Finally, we assessed the expression of alphaVbeta1 in different human tissues and primary human fibroblasts and demonstrated the upregulation of alphaVbeta1 heterodimer in human fibrotic diseases.
Conclusion: Novel mechanisms have been unveiled for the role of alphaVbeta1 integrin in liver fibrosis. Inhibition of alphaVbeta1 impairs HSC migration in vitro and ameliorates fibrosis in a mouse NASH model. The genes modulated by the alphaVbeta1 inhibitor in animals share common signatures that are dysregulated in human NASH liver with advanced fibrosis. AlphaVbeta1 represents a promising target for liver fibrosis.

FRI248

AlphaVbeta6 inhibitor stabilizing the bent closed integrin conformation is effective in primary sclerosis cholangitis mouse model

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Background and Aims: Integrins are heterodimeric membrane proteins composed of alpha and beta subunits that regulate cellular activity by integrating the extracellular and intracellular environments in a bidirectional manner. Integrins can undergo large conformational changes in response to mechano-biochemical signalling events, differing in intracellular or extracellular ligand affinity by up to 1000-fold. AlphaVbeta6, an integrin highly expressed in injured biliary ductular cells, binds to latency-associated peptide (LAP) of transforming growth factor beta (TGF-beta) as its principal ligand and activates mature TGF-beta that drives fibrogenesis. Understanding the impact of conformations of alphaVbeta6 integrin stabilized by its inhibitors on disease pathophysiology may have implications in the therapeutic potential of this target class.
Method: Small molecule oral inhibitors that stabilize the alphaVbeta6 integrin in a bent-closed conformation have been identified. The efficacy of the small molecule closing inhibitor, MR-cpd3, was evaluated in a 0.1% DDC (3,5-diethoxycarbonyl-1,4-dihydrocollidine)-diet-induced primary sclerosing cholangitis (PSC)-like biliary mouse model. Feeding with a DDC diet for 7 days [for acute pharmacodynamics (PD)] or 20 days (for chronic efficacy) in 8-wk old mice was used to induce biliary fibrosis and cholestasis. MR-cpd3 was orally administered at 10–60 mg/kg, b.i.d., in both the acute and chronic DDC models to evaluate its anti-fibrosis effects. mrationTo understand the differential effects of conformation specific alphaVbeta6 inhibition, a closing antagonist and an opening antagonist were dosed at 10 mg/kg in DDC mice.
Results: In the chronic DDC-induced PSC model, MR-cpd3 treatment dose dependently reduced cholestatic end points and hepatic collagen deposition. While the expression of some fibrotic genes and plasma cholestatic markers were equally reduced by both opening and closing inhibitors, other critical genes, such as CTGF, and plasma total bile acid levels, were differentially modulated by the closing and opening inhibitors. In the acute PD model, gene set enrichment analysis (GSEA) of the RNAseq results revealed that closing antagonism of alphaVbeta6 distinctively modulates lipid metabolism and epithelial cellular proliferation while the opening compound did not.
Conclusion: Our results suggest that alphaVbeta6 inhibition ameliorates biliary fibrosis and markedly improves liver function in DDC-induced PSC model. AlphaVbeta6 presents as a high potential target in cholestatic liver diseases. The development of new generation of

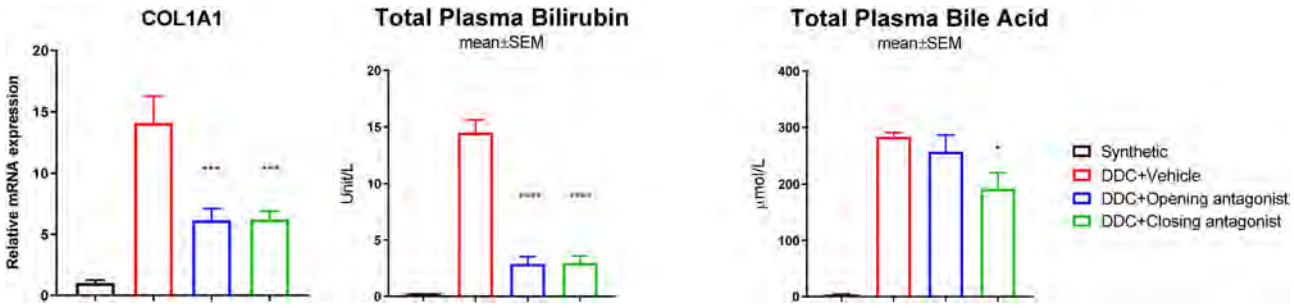

Figure: (abstract: FRI248)

oral drugs that stabilize the closed conformation of this integrin is desirable to realize this potential.

FRI249

Endotrophin, a hormone derived from type VI collagen, activates fibroblasts and drives fibrosis in the liver, lung, kidney, and heart

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Background and Aims: The type VI collagen pro-peptide, endotrophin (ETP), holds signaling properties in the extracellular matrix (ECM). Fibrosis may in some instances self-perpetuate in the absence growth factors such as transforming growth factor (TGF)-β and platelet-derived growth factor (PDGF). This suggests that ECM components produced by fibroblasts may drive fibrosis. We undertook a systemic screening approach to identify fragments of collagens that could induce fibrosis in fibroblasts to the same extent as TGF-β. In addition, we investigated serological collagen biomarkers and their association to fibrosis in prospective cohorts of liver, lung, kidney, and heart fibrosis in a meta-analysis.
Method: The effect of ETP, TGF-β and PGDF-DD was investigated on type III collagen formation in a scar-in-a-jar (SiaJ) cell model using human fibroblasts. Cells were exposed to 11.75 nM human recombinant ETP. In a meta-analysis, serum samples from patients with liver cirrhosis and hepatocellular outcome (HCC) (n = 200), acute-on-chronic liver failure (ACLF) (n = 150), chronic kidney disease (n = 500), heart failure (n = 350), idiopathic pulmonary fibrosis (IPF) (n = 300) were included. Biomarkers of type III formation (PRO-C3) and ETP (PRO-C6) were assessed in cell supernatants and patient sera by ELISAs developed at Nordic Bioscience.
Results: In SiaJ, PRO-C3 was increased 700% when induced by ETP ($p < 0.0001$) comparable to TGF-β and PDGF-DD induction. PRO-C6 was correlated to disease severity of liver, lung, and kidney fibrosis and SSC. Baseline PRO-C6 predicted 1) worsening of liver fibrosis in liver biopsies, progression from cirrhosis to HCC, liver related outcome, and outcome of ACLF; 2) progression of IPF defined by a decline in forced vital capacity (FVC) > 10% or death; 3) Kidney fibrosis and function loss defined as a decline in eGFR, progression to end-stage renal disease, and death; and 4) heart failure, hospitalization or death.
Conclusion: Here we show that ETP have a direct stimulating effect on fibroblasts. These data are the first to suggest that collagen peptides initiate and drive fibrosis, independent of TGF-β and PDGF. Moreover, ETP was prognostic for all fibrotic diseases tested, suggesting ETP to be a common denominator for progression of fibrosis and outcome. Further understanding of this signal may lead to novel treatments of fibrosis.

FRI250

Hepatocytic C-jun NH2 terminal kinase activity confers protection against cholestatic liver injury in mice

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Background and Aims: Chronic liver injury triggers death of parenchymal cells, followed by an inflammatory response activating myofibroblasts eventually leading to liver fibrosis. C-Jun NH2-terminal kinase (JNK) activation plays a crucial role during hepatic fibrosis progression. Previously, we showed that JNK1 in hepatic stellate cells (HSCs) mediates transactivation of HSCs during murine liver fibrosis. Moreover, JNK combined activities are fundamental for drug-induced liver injury. In the present work, we investigated the functional of Jnk1/2 in hepatocytes during cholestatic liver disease.
Method: The involvement of JNK in the pathogenesis of human and murine cholestatic liver diseases (CLD) was examined. Cholestatic liver injury was triggered through 28 days bile duct ligation (BDL) in $Jnk1^{f/f}/2^{f/f}$ (WT) and $Jnk1/2^{\Delta hepa}$ (hepatocyte-specific deletion of JNK1 and JNK2) mice. The states of liver injury, inflammation and fibrosis were investigated. Moreover, microarray analysis was performed.
Results: Analysis of liver sections from patients with primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) with varying degrees of hepatic fibrosis revealed strong JNK activation in both immune and parenchymal cells compared to healthy control livers correlating with disease activity. Additionally, JNK activation was characteristic in the livers of murine cholestasis ($Mdr2^{-/-}$ and BDL). After 28 days of BDL, $Jnk1/2^{\Delta hepa}$ compared to WT mice developed a significantly severer phenotype as characterized by exacerbated serum transaminases, increased ductular proliferation and dramatically increased areas of bile infarcts. Consistently, liver analysis revealed increased hepatic fibrogenesis, oxidative stress and inflammation in $Jnk1/2^{\Delta hepa}$ compared to WT mice, 28-days after BDL. Microarray analysis indicated that $Jnk1/2^{\Delta hepa}$ livers displayed increased transcripts of genes related to IL-6 signaling and mucosal and epithelium protection (Trefoil and Mucin).
Conclusion: JNK is strongly activated during human and murine cholestatic liver injury. Combined JNK function in hepatocytes

confers protection during cholestatic liver injury-induced liver fibrosis and thus our study defines a novel therapeutic target for CLD.

FRI252

Novel Rho associated coiled kinase inhibitor improves hepatic fibrosis in mice model of non-alcoholic steatohepatitis (NASH)

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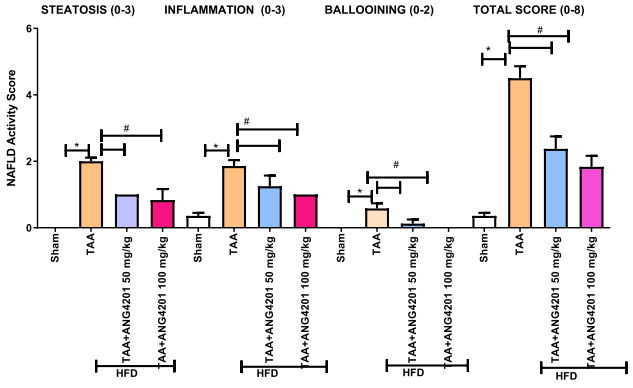
Background and Aims: Rho-associated coiled kinases 1 (ROCK1) and 2 (ROCK2) are involved in variety of cellular processes including tissue fibrosis. Recently, we demonstrated that hepatic ROCK2 and not ROCK1 is upregulated in mice model of NASH (thioacetamide + high fat diet). The present study was done to investigate if selective blocking of ROCK2 reduces hepatic fibrosis and improves liver function.

Method: Using core hopping and structure based drug design approach, we synthesized highly selective (>200 fold selective for ROCK2 vs ROCK1), orally bioavailable ROCK2 inhibitor (ANG4201). We evaluated the antifibrotic effects of ANG4201 in mice model (C57Bl/6) of NASH. Adult male and female mice were subjected to high fatty diet (FFD) for three months and thioacetamide (TAA, 100 mg/kg body wt) was administered thrice a week concomitantly to accelerate the progression of liver fibrosis. After three months, mice were randomized to vehicle or ANG4201 (50 & 100 mg/kg body wt, PO, BID) for two-months. Liver injury was analysed by measuring serum transaminases (AST/ALT). RNA was isolated from livers and panel of fibrotic and inflammatory markers were assessed by RT-PCR. Collagen quantification was performed on liver tissue using Bioquant software.

Results: Compared to control, ANG4201 treatment dose dependently reduced TAA + FFD induced liver fibrosis in mice, demonstrated by significant reduction in hepatic hydroxyproline, Masson Trichrome and Sirius red staining as well as alpha-SMA, collagen I, CTGF and TGF-beta mRNA expression and the inflammatory infiltration and myofibroblast activation associated-signalling (TNF-alpha, FN1 and MMP3). The reduction in fibrosis was associated with significant improvement in the ratio of liver wt and body wt and reduction in serum transaminases. ANG4201 treatment was associated with overall improvement in NAFLD activity score.



Conclusion: This study demonstrates that ROCK2 upregulation contributes to hepatic fibrosis and hepatic dysfunction in FFD+TAA mice model. ANG4201 is highly promising orally bioavailable therapeutic ROCK2 inhibitor with potential use in liver fibrosis.

FRI253

Non-invasive test cut-offs for the identification of advanced liver fibrosis in a diabetes cohort with non-alcoholic steatohepatitis: data from the phase 3 AURORA study

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Background and Aims: In NASH patients, type 2 diabetes (T2D) is a driver of liver fibrosis progression and related complications. Pre-test probability of disease heavily influences the performance of non-invasive tests (NITs), so their predictive value may be degraded in T2D patients. Use of more advanced NITs (eg, transient elastography, ELF) to identify T2D patients with high fibrosis risk may not be economically and technically feasible. There are no cut-off points for NITs applicable solely to T2D populations to inform healthcare providers of the need for referral to a hepatologist and/or to a clinical trial. We aimed to identify cut-off points for simple NITs in patients with T2D with NASH at risk of liver fibrosis.

Method: Screening visit data from T2D patients with biopsy-confirmed NASH from the Phase 3 AURORA trial were analysed to determine the cut-off values for the target fibrosis stages (F3–F4, NASH CRN) based on FIB-4, APRI, and NFS. The predictive accuracy of each NIT was evaluated using logistic regression. Subjects were classified into binary responder groups: F3 and F4 were considered positive; F0 to F2 negative. Positive and negative predictive values (PPVs and NPVs) were obtained to identify cut-offs that had acceptable specificity and PPV to rule in advanced fibrosis. NPV ≥ 30% and PPV ≥ 80% were used to detect those cut-offs.

Results: The AURORA screening database included 2056 subjects with NASH who underwent liver biopsy; of those, 420 subjects with T2D were included in this analysis (17, 86, 121, 170 and 26 had fibrosis staging F0, F1, F2, F3 and F4, respectively). The AUROCs for FIB-4, APRI and NFS were 0.68, 0.67 and 0.56 for F3–F4, respectively. In NASH patients with T2D and F3–F4 liver fibrosis, cut-off value for FIB-4 was ≥2.31 (sens 0.21, spec 0.96, PPV 0.80, NPV 0.58) and for APRI was ≥1.03 (sens 0.20, spec 0.96, PPV 0.81, NPV 0.58).

Conclusion: The cut-off points for FIB-4 and APRI for F3–F4 derived from the large AURORA study screening cohort may serve to identify T2D patients who definitely need hepatologist referral and/or considered for enrolment in clinical trials. Further validation using other cohorts to refine predictive values in respect of varying pre-test probabilities and contexts of use is warranted. Editorial assistance by Complete HealthVizion.

FRI254

What did we learn from a large cohort of more than 24,000 patients evaluated by transient elastography in a single- center?

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Background and Aims: In the last years, transient Elastography (TE) became one of the main tools for the non-invasive assessment of liver fibrosis. The aim of our study was to assess the feasibility of TE and fibrosis stage prevalence, evaluated by TE, in a large cohort of patients in a single study centre.
Method: We performed a retrospective study on 24,454 liver stiffness measurements (LSM) by mean of TE performed in our Department during a 12 years period (2007–2019). The study included patients with liver diseases of various etiologies and normal subjects. In each patient, 10 valid LSM were obtained using the M or XL probe, according to the body mass index (BMI) of each subject. If no valid LSM could be obtained, the evaluation was declared as failed. Reliable LSM were defined as median value of 10 measurements with Interquartile range/median (IQR/M) ≤ 30%, and a Success Rate (SR) ≥ 60%. To discriminate between liver fibrosis stages by TE we used the following cut-offs [1]: F2-7 kPa; F3-9.5 kPa and F4-12 kPa.
Results: Gender distribution was relatively equal, with 49.9% (11,223 female subjects), average age 54 years. LSM were obtained using the M probe in 72.2% (17,663) cases and by XL probe in 27.8% (6,791) cases. The feasibility in our cohort was 90.7%; 2,270 of the 9.3% LSM (24,454) were considered failed or unreliable. The etiology of chronic liver diseases evaluated by TE was: hepatitis C virus infection: 35%, hepatitis B virus infection: 20.6%, dual hepatitis virus infection: 1.4%, alcoholic liver disease: 5.4%, Non-Alcoholic Steatohepatitis (NASH): 6.8%, Both Alcoholic and Non-Alcoholic Steatohepatitis (BASH): 0.3% (81 patients), hepatocytolysis syndrome 4%, autoimmune hepatitis 0.8% (194 patients), normal subjects 2% (494 cases) and other etiologies: 23.7% (5,750 patients).
Based on TE cut-off values, the severity of liver fibrosis in our group was as follows: F < 2: 48.9% patients (10,851); F2: 15.5% patients (3,449); F3: 8.5% (1,886 patients) and F4: 27% patients (5,998).
Conclusion: Transient elastography had a feasibility of 90.7% in this large cohort, almost half of the patients (48.9%) having at most mild fibrosis, and a little bit over one quarter having cirrhosis (27%).

Reference:

1. Tsochatzis EA, Gurusamy KS, Ntaoula S et al. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a metaanalysis of diagnostic accuracy. *J Hepatol* 2011;54:650–659

FRI255

The impact of LOXL2 inhibition on fibrosis progression in-vitro and in-vivo

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Background and Aims: Fibrosis is the final common pathway of chronic liver injury, and resultant cirrhosis accounts for >2.5% of deaths worldwide. Lysyl oxidase-like protein 2 (LOXL2) oxidises lysine residues in collagen/elastin leading to stabilisation of the extracellular matrix. The aim of this study was to investigate whether LOXL2 enzyme inhibition would reduce fibrosis in models of liver disease.
Method: Models of hepatic fibrosis in mice and rats (CCl_4, *Mdr2*$^{-/-}$, TAA) were used to evaluate the efficacy of LOXL2 enzyme inhibitors (Pharmaxis) as assessed by flow cytometry, immunohistochemistry, qPCR and assessment of blood markers of liver injury. LOXL2 inhibition was assessed *in vitro* using primary human fibroblasts.
Results: LOXL2 inhibition reduced CCl_4-induced liver fibrosis in rats (median % picrosirius red area following 2 weeks treatment, vehicle 2.84% vs high dose inhibitor 1.90%, p = 0.02; vehicle vs low dose inhibitor 1.92% p = 0.07; qPCR: median expression for *Col1a1* following CCl_4 injury was, vehicle 0.021 vs low dose inhibitor 0.009, p = 0.006, or high dose inhibitor 0.003, p = 0.001, for *Acta2* vehicle 0.010 vs low dose inhibitor 0.004, p = 0.001, or high dose inhibitor 0.001, p < 0.0001).
This effect was not observed in either the short murine *Mdr2*$^{-/-}$ model of liver injury following administration of LOXL2 inhibitor on alternate days (median % fibrosis, vehicle 4.64% vs inhibitor 4.61%, p = 0.46; median *Col1a1,* vehicle 0.11 vs inhibitor 0.84, p = 0.27, *Acta2,* 0.0006 vs 0.0005, p = 0.98) nor in the longer and more fibrotic TAA model with daily gavage of LOXL2 inhibitor (median % fibrosis, vehicle 9.4% vs inhibitor 8.4%, p = 0.46, median *Col1a1,* vehicle 0.08 vs inhibitor 0.078, p = 0.53, *Acta2,* 0.00006 vs 0.00007, p = 0.69). Daily provision of LOXL2 inhibitor following cessation of TAA dosing did not accelerate resolution of TAA induced fibrosis, and was not associated with altered intrahepatic immune cell infiltration (median % fibrosis, vehicle 3.9% vs inhibitor 5.6%, p = 0.13, median *Col1a1*, vehicle 0.04 vs inhibitor 0.06, p = 0.43, *Acta2*, 0.0006 vs 0.0005, p = 0.95; median % CD4+ cells, vehicle 9.1% vs inhibitor 8.9%, p = 0.46), median % CD8+ cells vehicle 7.0% vs inhibitor 8.3%, p = 0.60).
Notably, LOXL2 inhibition reduced human fibroblast contractility *in vitro*, implicating the LOX family of enzymes in fibrosis progression (% contraction, control 81.5% vs inhibitor 67.3%, p = 0.004).
Conclusion: Inhibition of LOXL2 enzyme showed differing effects in rat, mouse and human models of liver disease. This suggests that the timing and dose of the inhibitor are critical for effective targeting of LOXL2 in different species.

FRI256

Hydrophobic bile acids promote proliferation and activation of hepatic stellate cells by PI3K-dependent mechanisms

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Background and Aims: Chronic cholestatic liver diseases frequently progress to liver fibrosis. In this context, hydrophobic bile acids (BA) are assumed to exhibit pro-fibrotic effects. However, mechanisms of cholestasis-induced liver fibrosis are incompletely understood. It has been described that BA may induce pro-proliferative signals in murine hepatic stellate cells (mHSC). Functional consequences of such signalling, however, have not been explored and underlying signalling pathways are unknown. We therefore investigated effects of BA on HSC proliferation, cell expansion and collagen deposition as well as contributing signalling pathways.
Method: mHSC derived from female FVB mice were isolated, purified and incubated with hydrophilic and hydrophobic BA. Activation of signalling pathways was evaluated by western blotting. Cell proliferation was determined via BrdU assays. Total cell count was evaluated microscopically, DNA quantification served as alternative measure for cell mass. Collagen deposition was quantified photometrically. The human stellate cell line LX2 was incubated with TGF beta and activation was determined by alpha SMA quantification.
Results: The most relevant hydrophobic BA in human cholestasis, chenodeoxycholic acid (CDCA), but not cholic acid and ursodeoxycholic acid, led to an increased proliferation of mHSC in BrdU assays, which led to an increased cell count after 14 days of culture. HSC mass increased dose dependently to up to 1.90 ± 0.9-fold (0.25 mM CDCA, mean ± SD, p < 0.05). Accumulation of mHSC resulted in increased deposition of collagen. These effects were associated with phosphorylation of protein kinase B (PKB) after shortterm (2–4 h) and longterm (7–10 d) stimulation. Inhibition of the upstream target

PI3 K by LY294002 (0.01 mM) impeded CDCA induced phosphorylation of PKB and prevented BA-induced HSC cell expansion. Suggesting a role of this signalling pathway also in humans, TGF beta-induced activation of LX2 cells was abolished by LY294002.
Conclusion: Hydrophobic but not hydrophilic BA induce pro-proliferative signalling in murine HSC. We describe for the first time that such signalling is associated with consecutive cell mass expansion and collagen deposition. These pro-fibrotic effects may partially be mediated by PI3 K dependent signalling. Activation of human HSC, too, may be mediated by PI3 K.

FRI258

Aldafermin (NGM282) reduces the cross-linked pro-peptides of type III collagen PRO-C3X, a novel biomarker, in non-alcoholic steatohepatitis and primary sclerosing cholangitis patients

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Background and Aims: Cross-linking of collagen is a key contributor to tissue stiffness. Recent studies have shown that circulating concentrations of PRO-C3X are elevated in HCC patients, and are superior to PRO-C3 in predicting progression-free survival and overall survival independent of AFP (Jensen et al., 2019). Aldafermin (NGM282), a non-tumorigenic FGF19 analogue, is a potent regulator of bile acid synthesis with anti-fibrotic effects in clinical trials. We determined plasma levels of PRO-C3X in phase 2 trials of aldafermin in NASH and PSC.
Method: Fourty-three NASH subjects, with NAS ≥4 (at least 1 point in each component), stage 1–3 fibrosis and absolute liver fat content by MRI-PDFF ≥8%, received aldafermin 1 mg or 3 mg daily for 12 weeks (W12). 62 PSC subjects, with an elevated ALP>1.5xULN at baseline (BL), received aldafermin 1 mg, 3 mg or placebo daily for 12 weeks. The PRO-C3X sandwich ELISA only detects cross-linked type III collagen pro-peptides, whereas the PRO-C3 competitive ELISA quantifies the sum of single-stranded and cross-linked pro-peptides (Nordic Bioscience).
Results: At BL, circulating PRO-C3X concentrations were significantly lower in subjects with NASH than PSC (9.1 ng/mL vs 14.7 ng/mL, $p < 0.001$), while PRO-C3 levels were similar in NASH and PSC. PRO-C3X declined rapidly and significantly with aldafermin therapy in NASH (−2.7 and −2.8 at W6 and W12 in the 1 mg group, $p < 0.001$ vs BL for both comparisons) and PSC (−0.8 and −0.7 at W2 and W12 with aldafermin 1 mg; −2.8 and −3.1 at W2 and W12 with aldafermin 3 mg; $p < 0.01$ vs BL for all comparisons) (Table 1). In contrast, no significant change in PRO-C3X was observed with placebo (0 and +0.5 at W2 and W12 in PSC).
Conclusion: NASH patients had much lower type III collagen cross-linking than PSC patients, underlining the potential for rapid fibrosis reversal in a dynamic extracellular matrix environment in NASH. Aldafermin significantly reduces PRO-C3X, a novel noninvasive marker of cross-linked type III collagen, across metabolic and cholestatic liver disease. Given that liver fibrosis progression and HCC growth are associated with matrix stiffness and cross-linking of collagens, these results may support an anti-tumor activity, in addition to the anti-fibrotic activity, of aldafermin in chronic liver disease.

Table 1: Aldafermin reduced cross-linked type III collagen in NASH and PSC populations.

	PRO-C3X (ng/mL)				
	BL	W12	Change from BL at W12	P (vs BL)	P (vs Placebo)
NASH Population					
Aldafermin 1 mg	9.9	7.2	−2.8	<0.001	NA
Aldafermin 3 mg	7.9	6.7	−1.2	0.07	NA
PSC Population					
Placebo	15.8	16.1	0.5	0.62	
Aldafermin 1 mg	14.2	13.3	−0.7	0.004	0.008
Aldafermin 3 mg	14.3	10.9	−3.1	0.001	0.006

FRI259

Small extracellular vesicles from mesenchymal stem cells pre-conditioned with interferon-? can improve liver fibrosis by inducing anti-inflammatory macrophages with high migratory and phagocytotic abilities

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Background and Aims: The effect of γ-sEVs on macrophage polarization, motility, and phagocytosis were evaluated *in vitro*. To analyze the contents of γ-sEVs, proteomics and miRNA analyses were performed. To analyze the effects of γ-sEVs, hepatic stellate cells (HSCs) were cultured with sEVs. To evaluate the therapeutic effects, a cirrhosis mouse model was treated with MSCs and sEVs with or without IFN-γ. To assess the effects of sEVs in the liver, single-cell RNA sequencing of immune cells, including macrophages in the liver tissues, was performed.
Method: The effect of γ-sEVs on macrophage polarization, motility, and phagocytosis were evaluated *in vitro*. To analyze the contents of γ-sEVs, proteomics and miRNA analyses were performed. To analyze the effects of γ-sEVs, hepatic stellate cells (HSCs) were cultured with sEVs. To evaluate the therapeutic effects, a cirrhosis mouse model was treated with MSCs and sEVs with or without IFN-γ. To assess the effects of sEVs in the liver, single-cell RNA sequencing of immune cells, including macrophages in the liver tissues, was performed.
Results: γ-sEVs can effectively induce anti-inflammatory macrophages *in vitro* and enhance their motility and phagocytotic ability. Proteomics and miRNA analyses of MSC-derived exosomes revealed that some proteins, such as annexin-A1, and miRNAs were increased after IFN-γ stimulation. However, γ-sEVs did not inhibit the activation of HSCs *in vitro*, suggesting that γ-sEVs do not directly inhibit HSC activation. Furthermore, γ-sEVs contributed to a reduction in inflammation and fibrosis in the cirrhosis mouse model. The single-cell RNA sequencing analysis revealed a wide range of effects, such as induction of anti-inflammatory macrophages and regulatory T cell, which were observed in the liver.
Conclusion: γ-sEVs can act as "cargo" and induce anti-inflammatory macrophages with high migratory and phagocytotic abilities, thereby effectively reducing inflammation and fibrosis. Our results demonstrate that sEVs can be modified before treatment and can potentially be used to develop new therapeutic approaches for treating cirrhosis.

FRI260

Aspirin induces autophagy and alleviates liver fibrosis by reducing oxidative stress and inflammation in mice model of chronic liver injury

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Background and Aims: Aspirin has potent anti-platelet activities and possibly helps regression of fibrosis. We investigated the potentials and putative mechanisms of antifibrotic effects of aspirin in the liver using integrated omics analysis.
Method: C57/B6 mice were treated with CCl_4 for 8 weeks, followed by aspirin treatment. The identified antifibrotic targets were validated subsequently in mice and human samples with increasing grade of fibrosis.
Results: Biochemical and histopathological changes and hepatic fibrosis was greater in the CCl_4-treated (Group A) compared to CCl_4-Aspirin (CCl_4-ASA, Group B) group ($p < 0.05$) or controls (Group C). The proteome (>450 up- and >340 downregulated proteins) and metabolome (>70 up- and >60 downregulated metabolites) of Group-A was distinctly different compared to Group B or C ($p < 0.05$). Aspirin treatment significantly induced proteins and metabolites linked to drug and fatty acid metabolism, glutathione metabolism, autophagy, energy metabolism and amino acid metabolism ($p < 0.05$). In Group A, mice displayed down-regulation of autophagy related proteins such as lysosomal membrane associated protein 1 (LAMP1; <1.5 FC) whereas aspirin treatment significantly increases the expression of autophagy related proteins in Group B mice (LAMP1; >1.5 FC). Inflammatory pathways; TNF-alpha, NFKB signaling, arachidonic acid metabolism, cholesterol metabolism, synthesis of ketone bodies and butanoate metabolism were significantly reduced in Group B ($p < 0.05$). Global cross-correlation and clustering analysis showed significant association of differentially regulated pathways with biochemical parameters and markers of fibrosis (Sirius red, TGF-β) ($r^2>0.5$, $p < 0.05$). Protein-metabolite network analysis identified urea cycle (Arginase-1; ARG1), leukotriene metabolism (Arachidonate 5-lipoxygenase; ALOX5), oxidative-stress (Ryanodine receptor 2; RYR2) and tryptophan metabolism (Kynurenine-3-Monooxygenase; KMO) pathways which correlated with α-SMA, PDGFR-β and the degree of liver fibrosis ($r^2>0.75$, $p < 0.05$) and were inhibited with aspirin.

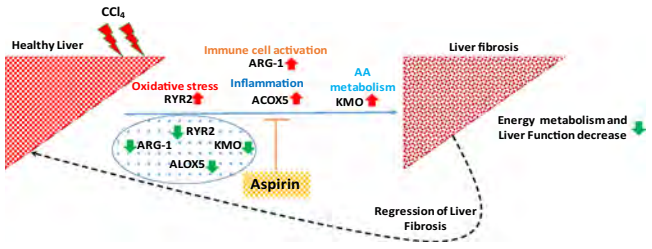

Figure 1 Aspirin mediated decrease in key marker proteins (RYR2, ALOX-5, ARG-1, and KMO) correlates with reduction of liver fibrosis and diseases severity.

Conclusion: Aspirin is effective in regression of hepatic fibrosis in the CCl_4 mouse model. It achieves this by enhancing autophagy and via inhibition of oxidative stress (RYR2), inflammation (ALOX5), urea cycle (ARG1) and tryptophan metabolism (KMO). Aspirin and targets for new identified molecules may serve as new therapeutic options for regression of hepatic fibrosis.

FRI261

Carabin deficiency promotes liver fibrosis via regulating RAS and calcineurin pathway in macrophage

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Background and Aims: Liver fibrosis a typical wound-healing response to chronic injury of variety etiologies, which can develop to cirrhosis and carcinoma. Carabin, an endogenous inhibitor of calcineurin (CaN) and Ras, its role in adaptive immune response has been documented, however, much less is known about its role in cells of the innate immune system such as macrophage.
Method: We induced experimental liver fibrosis in mice by intraperitoneal injection of 10% carbon tetrachloride (CCL4) twice a week for 8 weeks. To investigate the role of Carabin in the progression of liver fibrosis, we generated Carabinfl/fl LysMcre mice. Following the establishment of the fibrotic mouse model, hepatic macrophages were isolated.
Results: Carabinfl/fl LysMcre mice exposed to CCl4 were more susceptible to inflammation and fibrosis compared to wild-type counterparts. Carabin invalidation in myeloid cells is enhance inflammation and fibrosis progression. Cultured macrophages from Carabinfl/fl LysMcre mice displayed increased cytokine secretion and polarized toward to M1 or $Ly6^{hi}$ macrophage. Further studied demonstrated that Carabin regulatory macrophage polarization via inhibiting Ras and Calcineurin pathways.
Conclusion: Our findings suggest that Carabin plays a crucial proinflammatory role in liver fibrosis by regulating the Ras and Calcineurin pathways in macrophages and therefore may be a potential therapeutic target for immune-mediated liver fibrosis.

FRI262

(pro)renin receptor knockdown attenuates liver fibrosis through inactivation of ERK/TGF- ?1/Smad3 pathway

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Background and Aims: The (pro)renin receptor (PRR) activation upregulates the expression of profibrotic genes in kidney and heart. We aimed to investigate the role of PRR in hepatic fibrogenesis.
Method: Primary mouse hepatic stellate cells (HSCs) were isolated for PRR expression analysis. Human hepatic PRR levels were measured in patients with or without liver fibrosis. Experimental fibrosis was studied in thioacetamide (TAA)-treated or methionine choline-deficient (MCD) diet-fed C57BL/6 mice. Lentivirus-mediated PRR short hairpin RNA (shRNA) was used to knockdown hepatic PRR expression. A lentiviral vector expressing PRR shRNA from the α-smooth muscle actin promoter was used for HSC-specific gene knockdown.
Results: The PRR is upregulated in the mouse and human fibrotic livers and activated HSCs. Hepatic PRR knockdown reduced liver fibrosis with suppression of HSC activation and profibrotic genes expression in TAA-treated mice without significant changes in hepatic inflammation. The HSC-specific PRR knockdown also attenuated liver fibrosis in TAA or MCD diet-injured mice. Both the mice with HSC-specific and whole liver PRR knockdown down-regulated the hepatic ERK1/2-TGF-β1/Smad3 pathway. Renin or prorenin induced an increase expression of PRR and production of TGF-β1 in LX-2 cells and knockdown of PRR inactivated LX-2 cells with blocking production of TGF-β1 and Smad3 phosphorylation.
Conclusion: (Pro)renin receptor is upregulated in fibrotic livers and activated HSCs, and its downregulation attenuates liver fibrosis through inactivation of ERK1/2-TGF-β1/Smad3 pathway. Thus, PRR is a promising therapeutic target for liver fibrosis.

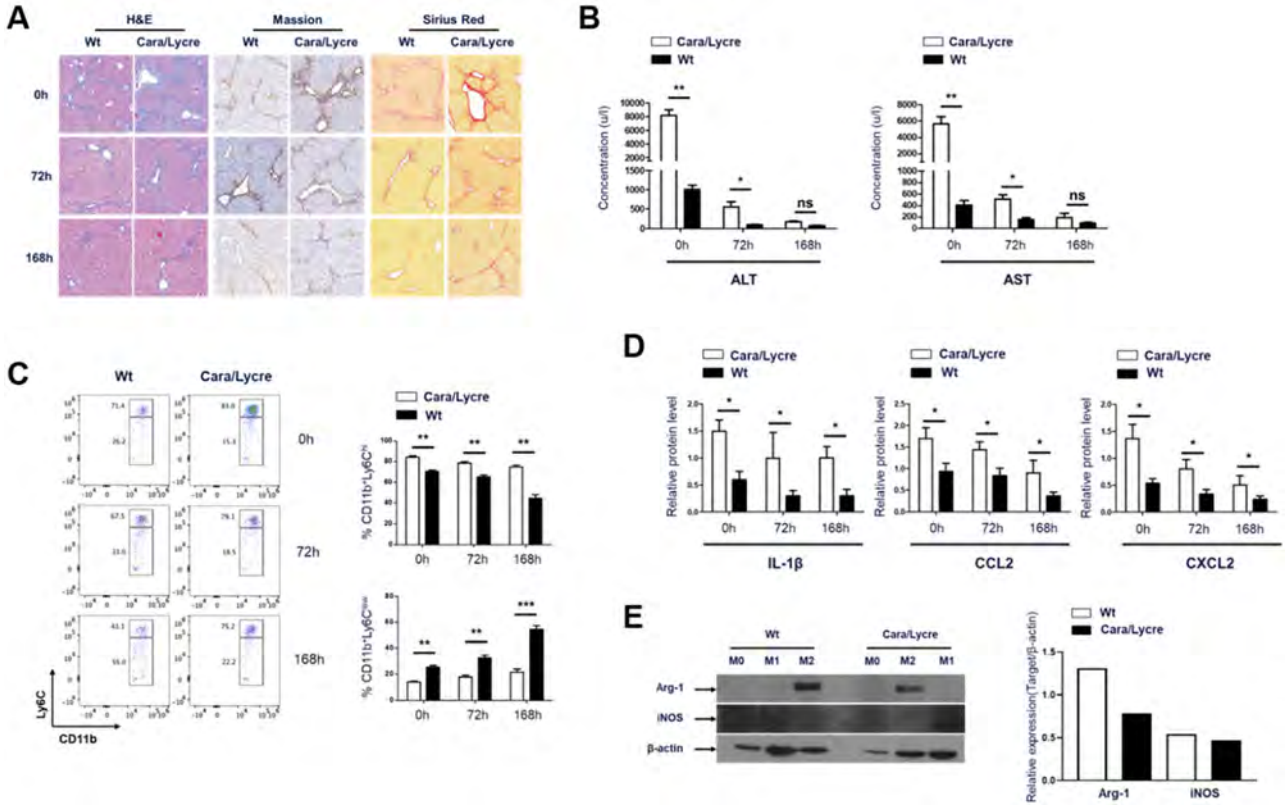

Figure: (abstract: FRI261)

FRI263

Diagnostic accuracy of liver stiffness measurement by fibroscan in liver transplant recipients

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Background and Aims: Vibration-controlled transient elastography (TE), is a non-invasive technique, measure the controlled attenuation parameter (CAP) for hepatic steatosis and liver stiffness for liver fibrosis. However, increased body mass index, hepatic steatosis, low fibrosis stage (<2) and the degree of hepatic necroinflammation affect liver stiffness measurement. The aims of the present study were to evaluate utility of TE for assessment liver fibrosis in liver transplantation (LT) recipients and compare the TE and the FIB-4, the APRI results.

Method: Between September 10, 2019 and November 9, 2019, a total of 106 consecutive LT recipients (M/F: 59/47) who had at least 1-year follow-up period underwent liver stiffness measurement by FibroScan with M or XL probe (Echosens, Paris, France). At least ten valid measurements were obtained within 5–10 minutes. APRI and FIB-4 scoring systems were also performed for the evaluation of liver fibrosis in the same time.

Results: The median time interval between LT and FibroScan was 78 months. The cause of LT was HBV-induced cirrhosis in 51 patients (48.1%), cryptogenic cirrhosis in 13 patients (12.3) and HCV-induced cirrhosis in 7 patients (6.6%). Living donor LT was performed on 74 patients (70%) and the remaining 32 had cadaveric donor LT. At the time of the evaluation, the mean age was 55.8 ± 11.6 years, mean body mass index was 26.1 ± 4.5 kg/m^2, and 38% had diabetes mellitus, 26% hypertension, and 25% were current smoker. The median serum AST, ALT and GGT levels were 22 U/L, 18.5 U/L and 29 U/L, respectively.

A median prevalence of 10 valid measurements (IQR) was 14% (4%–36%). The median CAP and liver stiffness values were 252.2 dB/m (range: 100–399) and 5.45 kPa (range: 2.1–30.3 kPa). The median FIB-4, APRI score were 1.44 (range: 0.15–3.92), 0.24 (range: 0.08–1.53) and the median platelet count was 198.500 (range: 50.000–471.000 per/ml), respectively.

A significant correlation among FIB-4, APRI and platelet counts (FIB-4 - APRI: $r = 0.74$, $p < 0.001$ and FIB-4 – platelet count: $r = 0.62$, $p < 0.001$, whereas no correlation was found between liver stiffness at TE and biochemical fibrosis tests (FIB-4 – TE: $r = 0.36$, $p = 0.72$ and APRI – TE: $r = 0.18$, $p = 0.61$).

Conclusion: Based on the results of the present study, liver stiffness measurement by FibroScan seems not to accurately assess graft fibrosis in liver transplant recipients.

Keywords: Liver stiffness, FibroScan, Liver Transplantation, FIB-4

FRI264

Improvements in the ELF test are associated with widespread changes in the hepatic transcriptome in patients with advanced fibrosis due to non-alcoholic steatohepatitis

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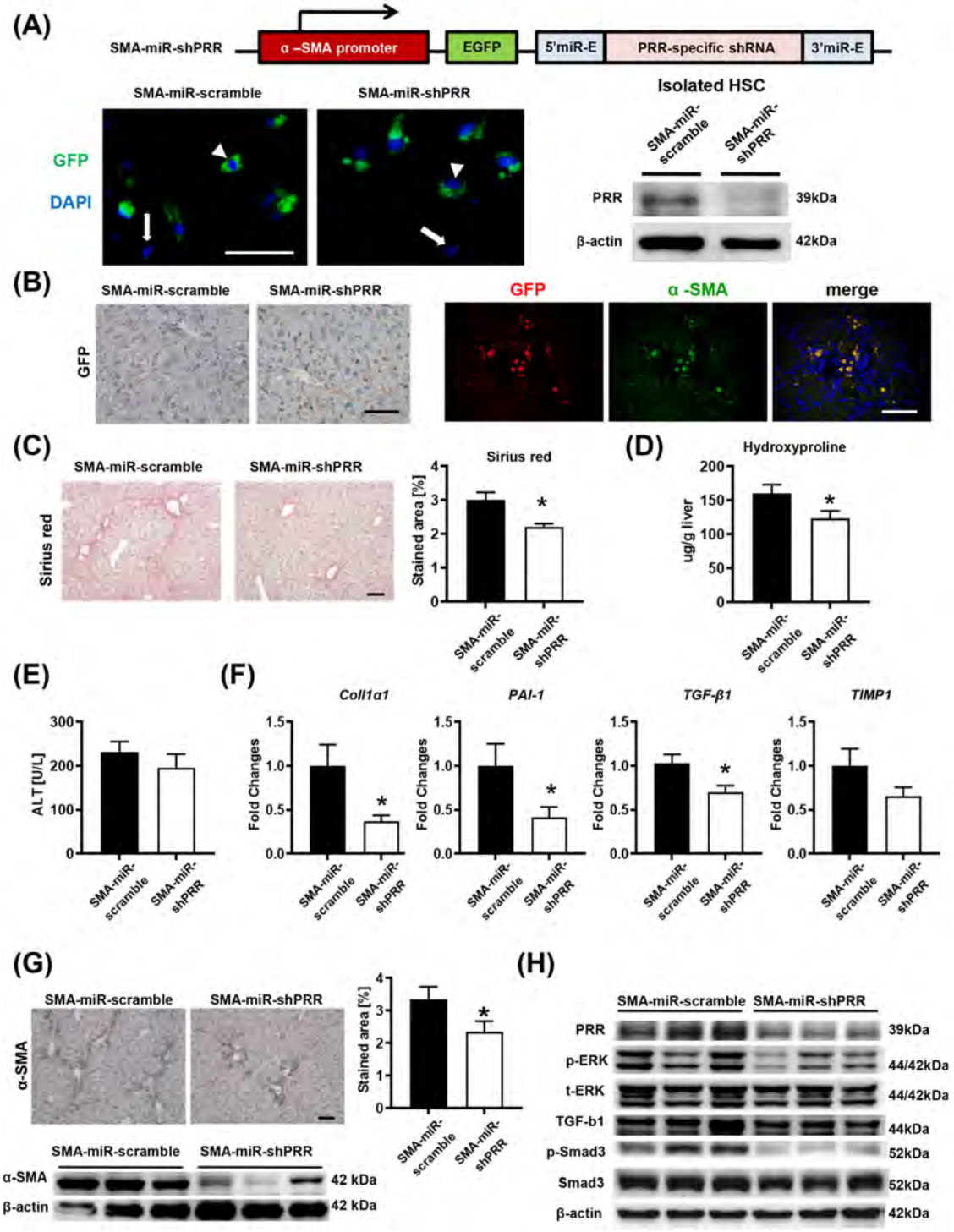

Figure: (abstract: FRI262): **Hepatic stellate cell-specific knockdown of PRR mitigated liver fibrosis in thioacetamide-injured mice.** Mice administered TAA were randomly received injections of lentivirus expressed PRR shRNA (n = 11) or scramble sequences (n = 9) under α-SMA promoter (labeled as SMA-miR-shPRR or SMA-miR-scramble, respectively).(A) The structure of lentiviral SMA-GFP-miR-PRR vector. Immunofluorescence images: HSCs isolated after lentiviral injection, arrowheads indicate GFP(+) cells and arrows indicate GFP(−) cells. Western blot of isolated HSCs confirmed knockdown of PRR. Scale bars = 50 μm. (B) HSCs-specific delivery was confirmed in vivo. Left: Immunohistochemical images of GFP in livers. Right: Immunofluorescence of GFP and α-sma. (C) Sirius red staining of liver sections with quantification. (D) Hepatic hydroxyproline levels. (E) Hepatic transcript levels of profibrotic genes. (F) Western blot and immunohistochemistry images of hepatic α-sma expression. (G) Western blot of PRR, phosphorylated and total ERK1/2, TGF-β1, phosphorylated Smad3 (p-SMAD3) and SMAD3 in mouse livers. *: P < 0.05 vs. the mice treated with TAA and SMA-miR-scramble virus. Scale bars = 100 μm.

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Background and Aims: The Enhanced Liver Fibrosis test (ELF) accurately stages fibrosis, is prognostic, and has potential for monitoring treatment response in patients with nonalcoholic steatohepatitis (NASH). Our objective was to evaluate changes in the hepatic transcriptome in patients with advanced fibrosis due to NASH according to improvement in the ELF test.

Method: Patients with advanced fibrosis (F3-F4) due to NASH (NAS ≥3) enrolled in two phase 3, placebo-controlled trials of selonsertib (STELLAR) were included. RNA was isolated from formalin-fixed paraffin-embedded (FFPE) blocks obtained from paired liver biopsies at baseline (BL) and week 48 (W48), sequenced using TruSeq® RNA Exome, and gene expression was quantified using Salmon. ELF was measured at BL and W48. Using Limma-Voom, we evaluated differential gene expression (adjusted p-value cutoff of 0.05) between patients with and without ELF response, defined as a ≥0.5-unit reduction from BL to W48. We overlapped differentially expressed genes with Hallmark gene sets curated by the Broad Institute (MSigDB Collection) and ascertained the significance of the overlap using hypergeometric distribution as implemented in the RITAN package.

Results: A total of 714 patients were included (median age 59 years, 60% female, 50% F4, median BL ELF 10.21 [IQR 9.59, 10.97]). An ELF response was observed in 17% (121/714) of patients (19% with F3 and 18% with F4), of whom 21 patients (17%) had a ≥1-stage improvement in fibrosis without worsening of NASH (histologic response). Differential expression of 486 genes was observed in patients with ELF response; 302 of these genes were also differentially-expressed in patients with histologic response. The cellular pathway that was enriched most significantly in patients with ELF response was related to pro-fibrogenic signaling ($q = 1.26 \times 10^{-20}$); additional enriched pathways are shown in the **Table**. The top differentially expressed genes in ELF responders (adjusted $p < 10^{-5}$) were *AKR1B10*, *LOXL4*, *THBS2*, *COL5A1*, *THY1*, *PDGFA*, *COL1A1*, *TIMP1* (all downregulated), *MT1E, MT1G,* and *GNMT* (all upregulated).

Table. Top differentially-enriched cellular pathways in patients with ELF response

Gene Pathway Enriched in ELF Responders (Number of Genes)	FDR q-value*	
	ELF Responders	Histologic Responders
Pro-fibrogenic signaling (37)†	1.26×10^{-20}	2.65×10^{-13}
Angiogenesis (8)	3.44×10^{-5}	9.25×10^{-9}
Myogenesis (18)	3.44×10^{-5}	2.84×10^{-2}
Apical junction (15)	8.44×10^{-4}	1.25×10^{-3}
KRAS signaling (15)	8.44×10^{-4}	--
p53 pathway (15)	8.44×10^{-4}	3.67×10^{-3}

* P-value adjusted for false discovery rate (FDR).
† Pathway referred to as epithelial to mesenchymal transition in Hallmark gene sets of the Broad Institute.

Conclusion: In NASH patients who experienced improvements in the ELF score, widespread changes in the hepatic transcriptome, particularly in pathways related to stellate cell biology and fibrosis, were observed. These data provide important insights into the pathogenesis of NASH and further support for the utility of the ELF test in monitoring treatment response in patients with advanced fibrosis due to NASH.

Imaging & drug targeting

FRI265

Contrast-enhanced ultrasound algorithms for the non-invasive diagnosis of hepatocellular carcinoma in high-risk patients - a prospective multicentre study (DEGUM-CEUS HCC trial)

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Background and Aims: Despite its high diagnostic accuracy for the non-invasive diagnosis of hepatocellular carcinoma (HCC) in high risk patients, standardisation of contrast-enhanced ultrasound (CEUS) is insufficient. This prospective multicentre study funded by the German Society for Ultrasound in Medicine (DEGUM) intended to improve standardisation of the CEUS examination procedure, and to assess the diagnostic value of CEUS and the new standardised CEUS-algorithms for non-invasive diagnosis of HCC.
Method: Patients at risk for HCC with histologically proven focal liver lesions upon B-mode ultrasound were prospectively assessed with CEUS following standardised examination protocols in 43 German centres. Clinical data, findings from B-mode ultrasound, CEUS, categorisation according to the CEUS algorithms ESCULAP and CEUS LI-RADS®, and histology were entered into online entry-forms. CEUS-based diagnosis was compared to histology as the reference standard.
Results: 395 patients (male/female = 329/66; mean age, 67.2 ± 10.5 years; liver cirrhosis, 76.5%) were enrolled. Mean tumour size was 57.6 mm (range, 5–200 mm; <2 cm, n = 42; 61.3% solitary). Histological diagnosis was HCC in 316 cases and intrahepatic cholangiocellular carcinoma (ICC) in 26 cases. 271 HCCs (85.8%) displayed arterial phase hyperenhancement; 255 (80.7%) showed contrast washout. The typical "hyper-hypo"-pattern was found in 72.2% of HCCs (positive predictive value, 87.4%), and the "hyper-iso"-pattern in 13.6% (positive predictive value, 86%). 33 HCCs (10.4%) showed late onset of washout after 4–6 minutes. Intensity of washout was mild in 54.7% and marked in 17.4% of HCCs. The highest sensitivity for the diagnosis of HCC was reached with the ESCULAP algorithm (94.2%) and subjective on-site interpretation of CEUS (90.2%). The CEUS LI-RADS® algorithm yielded the highest specificity (81.8%), but poorest sensitivity (61.8%) and negative predictive value (35.3%). The algorithms showed consensus in 67.1% of cases; 1/3 of the HCCs were correctly identified only with ESCULAP.
Conclusion: Arterial phase hyperenhancement is the key diagnostic feature of HCC in CEUS; positive predictive value of the hyper-iso-pattern is similar to that of the hyper-hypo-pattern. The standardised CEUS algorithms add little diagnostic benefit to conventional on-site interpretation of CEUS. Additional late phase assessment of washout after 4–6 minutes increases the diagnostic accuracy of CEUS for HCC and should be routinely performed.

FRI267

Evidence-based dilemma in the image-guided therapeutic management of uncomplicated amoebic liver abscess: a systematic review and meta-analysis

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Background and Aims: Amoebic liver abscess (ALA) continues to be a common problem in *tropical* countries. Role of adjunct ultrasound-guided percutaneous aspiration (PA) or percutaneous catheter drainage (PCD) in the treatment of uncomplicated ALA is still unclear. This systematic review and meta-analysis evaluated the available evidences with regard to image-guided treatment modalities in such patients.
Method: The database was searched for relevant randomized controlled trials (RCTs) comparing metronidazole alone versus metronidazole combined with PA or PCD, published till May 2019. All studies were assessed for risk of bias. The relevant data were pooled in a random or fixed-effect model to calculate the mean difference (MD) or relative risks.
Results: After the detailed screening, 570 patients from 10 RCTs comparing metronidazole alone with metronidazole combined with PA were included. Most studies had uncertain risk of biases. Days to resolution of abdominal pain (MD −1.59, 95% CI −2.77, −0.42, I^2 = 89%) and tenderness (MD −1.76, 95% CI −2.93, −0.58, I^2 = 72%) were significantly shorter in metronidazole + PA group. There was no significant difference in relation to the resolution of fever, abscess size and hospital stays. The beneficial effects of PA were seen with medium-to- large (>5 cm) ALA and not with small (<5 cm) ALA. Addition of PCD to metronidazole therapy was better than metronidazole alone in one low-quality RCT. Two RCTs found adjunct PCD to be better than PA for large ALA.
Conclusion: Metronidazole combined with PA, as compared to metronidazole alone, results in the early resolution of pain and tenderness in patients with medium-to-large ALA. PCD, as compared to PA, is better for drainage of larger ALA. However, discrepancies in RCTs create therapeutic dilemmas necessitating further efforts to generate more reliable data.

FRI269

Ph-responsive polymersomes for matrix metalloproteinase-1 delivery as a promising therapeutic strategy for the treatment of liver fibrosis

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Background and Aims: Liver fibrosis is a growing health problem affecting millions of people worldwide. Chronic liver injury leads to the formation of scar tissue due to the excessive accumulation of extracellular matrix, mainly collagen-I and -III produced by activated hepatic stellate cells (HSCs). Currently, there are no therapies available for liver fibrosis. Matrix metalloproteinase-1 (MMP1) is an enzyme that degrades the scar tissue by degrading collagen-I and -III favoring liver regeneration. We hypothesized that liver-specific delivery of MMP1 to degrade collagen as a promising approach for

Table: (abstract: FRI267): Response to Combined Therapy compared to Drug Therapy alone on Qualitative Parameters

Study	Early reduction of Fever &/or Leukocytosis	Early reduction of pain &/or tenderness	Early resolution of abscess size	Shorter Hospitalization	Remarks
Sharma MP	No	No	No	NS	Combined therapy not better
Blessmann J	No	No	Yes	NS	Minor benefit of combined therapy
A Tandon	Yes	Yes	NS	Yes	Combined therapy better
Van Allan	No	Yes	NS	No	Minor benefit of combined therapy
Bammigatti C	No	No	NS	No	Combined therapy not better
Widjaya P	NS	NS	Yes	NS	Combined therapy better
Freeman O	Yes	Yes	Yes	NS	Combined therapy better in abscess > 6 cm
Ghosh JK	Yes	Yes	Yes	NS	Combined therapy better
Arredondo CE	No	No	No	Yes	Combined therapy better
de la Rey Nel J	No	Yes	No	NS	Minor benefit of combined therapy

*NS: not stated

the treatment of liver fibrosis. Using state-of-the-art technologies, we synthesized innovative pH-responsive smart MMPsomes with the MMP1 decorated on the polymersome surface. Finally, we investigated the therapeutic efficacy of MMP1 and MMPsomes on human HSCs *in vitro* and on liver fibrosis mouse models *in vivo,* and *ex vivo* on fibrotic mouse livers.

Method: Polymersomes were fabricated using the pH switch method and MMP1 post-loading at pH 5–6 was performed to increase the interaction between MMP1 and the polymersome membrane. Physiochemical analysis and enzymatic assays were performed to characterize the attachment and functionalization of enzyme on polymersomes. *In vitro* studies were performed on TGF-beta-activated human HSCs to evaluate the effects of MMP1 and MMPsomes on the cell viability, gene and protein expression of collagen and HSCs activation marker alpha-SMA. Finally, the efficacy of MMP1 and MMPsomes was tested *in vivo* and *ex vivo* on CCl_4-induced liver fibrosis mouse models.

Results: Decoration of MMP1 on the surface of the polymersome was successfully established with an affinity of 30%, without inhibition of function. Synthesized MMPsome hybrid structures showed favorable size (~180 nm at pH 6 and ~140 nm at pH 8) and charge (positive at pH 6 and negative at pH 8). MMP1 and more significantly MMPsomes showed dose-dependent inhibition of collagen-I, -III and α-SMA gene expression, and collagen-I protein expression in TGFβ-activated human HSCs with no significant effects on cell viability. The studies on CCl_4-induced liver fibrosis mouse models have been performed, showed promising preliminary results with no *in vivo* toxicity however still under investigation.

Conclusion: In conclusion, we present an innovative approach of MMP1 delivery for the treatment of liver fibrosis.

FRI270

Diagnostic value of magnetic resonance elastography in cirrhotic portal hypertension

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Background and Aims: The liver and spleen stiffness may assess the severity of portal hypertension (PH) because of cirrhosis and

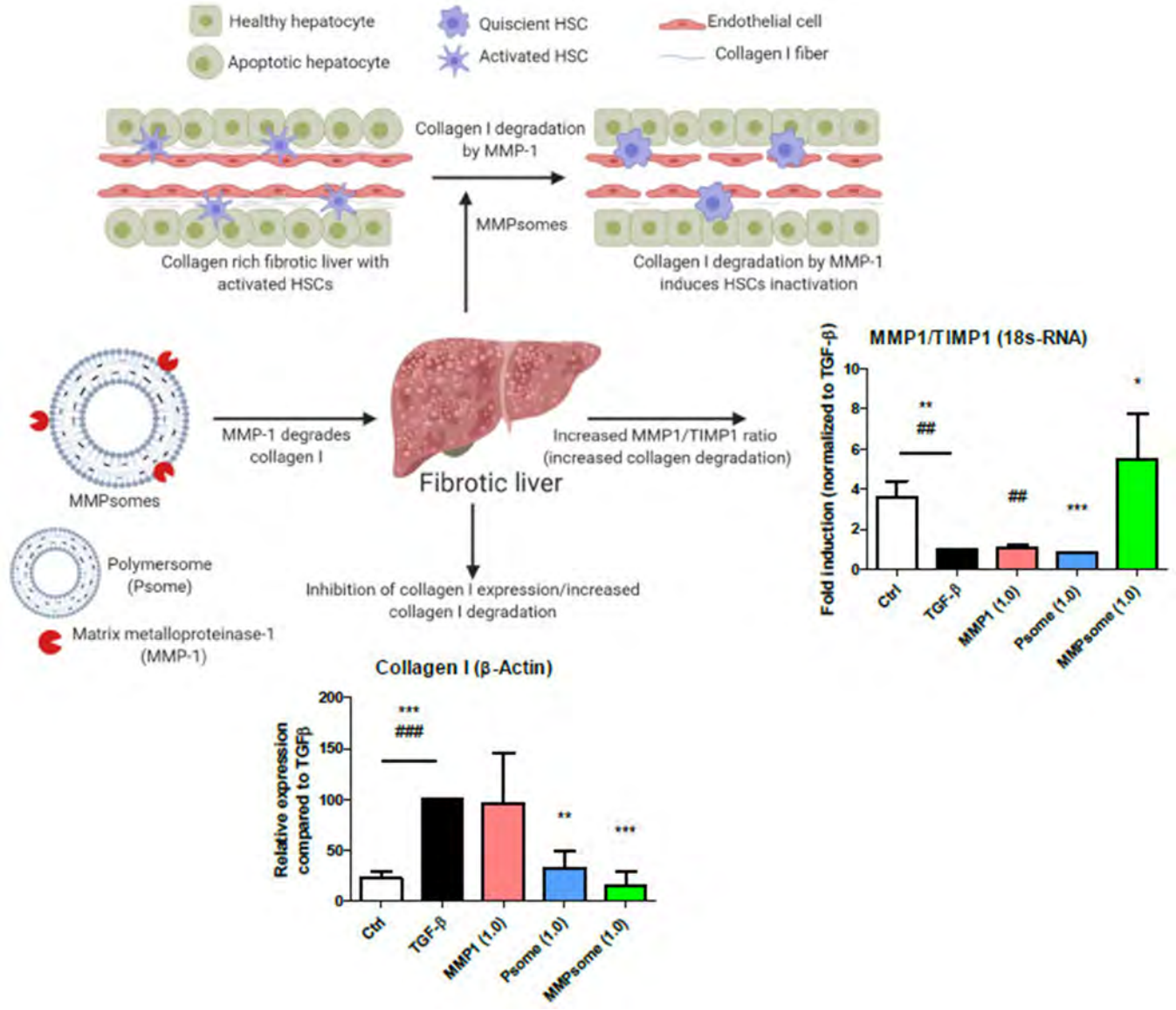

Figure: (abstract: FRI269)

splenomegaly. The aims of this study were to evaluate the diagnostic performance of magnetic resonance elastography (MRE) of the liver and spleen as a noninvasive tool for the severity of portal hypertension in cirrhosis.

Method: The patients with chronic liver disease who underwent hepatic vein pressure gradient (HVPG) measurements were consecutively enrolled in this study from November 2017 to October 2019 in Beijing Friendship Hospital, Capital Medical University. Liver stiffness (MLS) and spleen stiffness (MSS) were calculated by MRE within 1 week prior or inferior to HVPG measurement. The relationship between the liver or spleen stiffness values measured by MRE and the value of HVPG was assessed by using Spearman's correlation analysis. In addition, the diagnostic performances of MRE for predicting the presence of HVPG ≥ 12 mmHg, HVPG ≥ 16 mmHg and HVPG ≥ 20 mmHg were evaluated using area under the receiver operating characteristics curves (AUROCs).

Results: A total of 27 patients were included eventually (mean age: 53.3, 66.6% male). The main liver disease etiologies of the patients included in the study were Hepatitis B virus infection (25.9%)and alcohol (25.9%). There were five patients with HVPG < 12 mmHg and nine patients with HVPG ≥ 20 mmHg. MRE measurements of the liver and spleen stiffness was successfully performed on all patients. There was a significant correlation between spleen stiffness (r = 0.48, p = 0.012) and HVPG measurement. Liver stiffness-MRE was not significantly correlated with HVPG (r = 0.35, p = 0.076). The AUROC analysis is presented in the figure. To diagnose HVPG ≥ 12 mmHg using MSS, we observed AUROC of 0.782 (p = 0.006), sensitivity of 54.5%, and specificity of 100% (using cutoff ≥9.96). To diagnose HVPG ≥ 20 mmHg using MSS, we observed AUROC of 0.806(P < 0.001), sensitivity of 100%, and specificity of 63.2% (using cutoff ≥9.36).

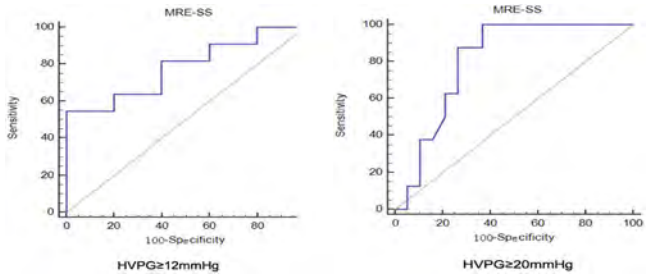

Figure The ROC curves of SS by MRE for the diagnosis of HVPG ≥ 12 and 20 mmHg.

Conclusion: MRE measurement of liver and spleen stiffness is feasible. MSS can diagnose HVPG ≥ 12 mmHg HVPG ≥ 20 mmHg well. But the sample size was small and our results need to be validated in a larger study.

FRI271

Prognostic value of spleen volume obtained from preoperative computed tomography images in patients with hepatocellular carcinoma

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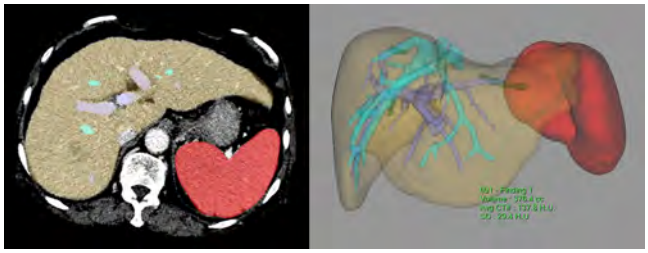
Background and Aims: Post-hepatectomy liver failure (PHLF) can occur as a major complication after hepatic resection (HR) for hepatocellular carcinomas (HCCs) and potentially affects the prognosis of patients. The development of PHLF is associated with portal hypertension and ensuing hepatic fibrosis, and portal hypertension is known to be associated with splenomegaly. Recently, it become possible to semi-automatically measure spleen volume using computed tomography (CT) images that are routinely obtained before HR in patients with HCC. However, the clinical importance of the spleen volume measured by using CT images has not been fully evaluated. Therefore, we aimed to assess whether spleen volume measured by using preoperative CT images could have a prognostic impact in patients who underwent HR for HCCs.

Method: We retrospectively enrolled 317 patients with very early or early HCCs who underwent preoperative CT and HR between January 2010 and December 2016. Spleen volume was semi-automatically measured by using the preoperative CT images. Receiver operating characteristics (ROC) curve and logistic regression analyses were performed to identify predictive factors for the development of PHLF. Cox proportional hazard model was used to determine prognostic factors for overall survival (OS).

Results: PHLF was observed in 72 patients (22.7%). The area under the ROC curve of spleen volume for the development of PHLF was 0.657 (p < 0.001). Multivariate logistic regression analysis revealed that operation time, extent of surgery, and spleen volume were associated with the development of PHLF. On survival analysis, serum prothrombin induced by vitamin K absence-II level, HCC size ≥8.6 cm, HCC differentiation, microvascular invasion, and spleen volume ≥214 cm^3 on preoperative CT were significant affecting factors for OS.



Conclusion: Spleen volume measured by using preoperative CT images was associated with the occurrence of PHLF and was a significant predictor for poor OS.

FRI272

Predicting prognosis of hepatocellular carcinomas according to treatments by using hepatobiliary phase images of gadoxetic acid-enhanced magnetic resonance imaging

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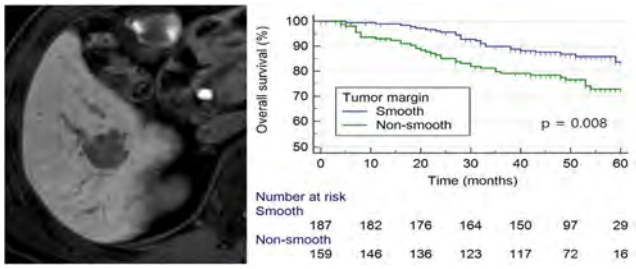
Background and Aims: The prognostic value of hepatobiliary phase (HBP) images of gadoxetic acid-enhanced magnetic resonance imaging (MRI) in patients with hepatocellular carcinomas (HCCs) according to treatments has not been investigated. Therefore, we aimed to predict prognosis in patients with HCCs after different treatments by using HBP images of gadoxetic acid-enhanced MRI.

Method: In this IRB-approved, single-institutional study, we retrospectively enrolled patients with very early or early, treatment-naïve HCCs who underwent gadoxetic acid-enhanced MRI between January 2014 and December 2015. A final cohort comprised of 347 patients with 381 HCCs that were pathologically proven (n = 130) or radiologically diagnosed (n = 251). Two radiologists evaluated the imaging features of HCCs and liver function on HBP images in consensus. Clinical findings were collected as well. Univariate and multivariate Cox proportional hazard models were used to reveal the predictive HBP imaging features of overall survival (OS).

Results: Following treatments were performed: resection (n = 130), radiofrequency ablation (RFA) (n = 96), and transarterial chemoembolization (TACE) (n = 121). Median and mean follow-up periods were 50.0 months (0–66 months, range) and 45.7 ± 15.7 months, respectively. Both in total patients and the resection group, among the HBP imaging features, non-smooth tumor margin (hazard ratio (HR) 3.202, 95% confidence interval [CI]; 1.042–9.839), satellite nodules (HR 3.336, 95% CI; 1.078–10.321), and tumor size (HR 1.023, 95% CI; 1.011–1.036) were shown to be associated with poor OS. In the RFA

group, liver-to-portal vein contrast (slightly hyper, HR 0.016, 95% CI; 0.002–0.781; hyper, HR 0.007, 95% CI; <0.001–0.778), and peritumoral hypointensity (HR 10.627, 95% CI; 1.483–76.134) were associated with OS. In the TACE group, tumor size was a predictor of poor OS (HR 1.014, 95% CI; 1.004–1.023). Among clinical findings, bilirubin, prothrombin time, creatinine, and alpha-fetoprotein were associated with OS.



Conclusion: Non-smooth tumor margin, satellite nodules, and larger tumor size on HBP images were independently associated with poor OS in both total patients and the resection group. Better liver function was associated with better OS in the RFA group, and larger tumor size was associated with poor OS in the TACE group.

FRI273

Kahweol activates Nrf2/HO-1 by a pathway different from p62 and autophagy dependent degradation

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Background and Aims: Kahweol is a coffee-specific diterpene found in coffee beans and present in unfiltered coffee drinks. Several studies demonstrated that kahweol induces Nrf2/HO-1 pathway. However, the mechanism by which kahweol increase Nrf2/HO-1 is unknown. Keap1 is one of the major regulators of Nrf2 expression and is known to be degraded mostly by autophagy. In this study, we investigated that kahweol is associated with a decrease in keap1 protein expression.

Method: Hepatocyte-specific ATG7 knockout mice were generated by crossing ATG7 Flox/Flxo mice with albumin Cre mice. We isolated and cultured ATG7K/O mouse primary hepatocyte, mouse primary hepatocyte and AML12 cells. The expression levels of HO-1, p62 and keap1 were measured by real-time RT-PCR analysis. The expression levels of HO-1, Nrf2, p62, keap1 and autophagye marker were measured by western blot analysis.

Results: Kahweol significantly increase HO-1, Nrf2 and p62 expression. In order to examine whether p62 mediates HO-1 expression because Nrf2- is activated by p62, siRNA targeting p62 was performed. Even if p62 is inhibited, kahweol still increases HO-1 expression. Next, we examined the effect of kahweol on keap1 expression. Kahweol decreased deap1 protein expression, but not decrease keap1 mRNA levels. To determine if kahweol degrades keap1, we examined ubiqutination and autophagy. Kahweol did not affect ubiqutination, but rather reduced autophagy-related proteins. In addition, kahweol also decreased keap1 protein expression in primary hepatocyte of ATG7 knockout mice.

Conclusion: This study shows that kahweol decreased keap1 protein expression in primary hepatocyte and AML12 cells. The keap1-Nrf2-pathway by p62 dependent autophagy is well known. However, it was confirmed that the reduction of keap1 by kahweol was not due to p62, ubiquitin and autophagy degradation. Further research is needed to determine whether kahweol regulates the translation of keap1.

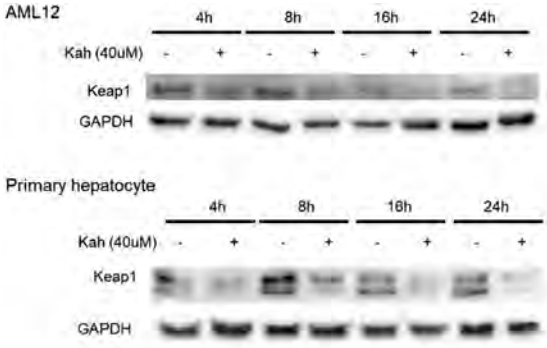

Figure. Kahweol reduces keap1 protein expression

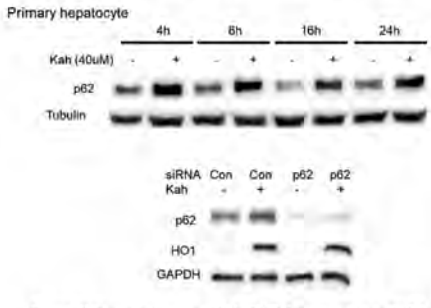

Figure. Kahweol increases p62, but HO-1 increase even if p62 decreases.

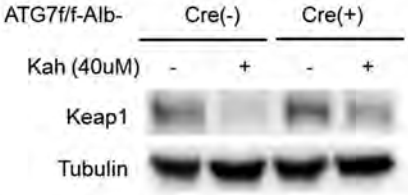

Figure. Kahwoel reduces keap1 in primary hepatocyte of ATG7 knockout mice.

Figure: (abstract: FRI273)

FRI274

Role of Kupffer phase image using sonazoid on CEUS LI-RADS® and diagnostic performance for hepatocellular carcinoma

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Background and Aims: The recently released contrast-enhanced ultrasonography Liver Imaging Reporting And Data System (CEUS LI-RADS) v2017 uses pure blood-pool agent only. This study aimed to evaluate CEUS feature using Sonazoid® for liver nodules with possibility for hepatocellular carcinoma (HCC) and to assess the diagnostic value of modified CEUS LI-RADS applied Kupffer phase image.
Method: This retrospective study included 228 patients at high risk for HCC who underwent CEUS using Sonazoid® between January 2013 and December 2016 in our tertiary institution. Total 235 nodules were classified as HCC group (n = 76) and indefinite HCC group (n = 159). HCC group is defined as pathologically proven HCC and/or CT/MRI LR-5; otherwise, classified into indefinite HCC group including LR-3/4 and LR-M. CEUS features were compared among two groups using t-test or Mann-Whitney test, and Chi-square or Fisher's exact test. And we have defined modified CEUS LI-RADS of which "Kupffer phase defect" is an alternative to "late and mild washout" of CEUS LI-RADS, and compared the diagnostic performance among two systems.
Results: The median nodule size on B-mode was 1.3 cm (range, 0.7–5 cm). Arterial phase hyperenhencement (88.2% vs. 73.0%, p = 0.009) were more frequent in HCC group than in indefinite HCC group. HCC group more frequently showed Kupffer phase defect (90.8% vs. 80.5%, p = 0.045) than indefinite HCC group, but there was no significant difference among two groups in late and mild washout (76.3% vs. 68.6%, p = 0.220). Modified CEUS LI-RADS showed higher sensitivity (80.3% vs. 69.7%), accuracy (70.2% vs. 68.1%), positive predictive value (52.6% vs. 50.5%), and negative predictive value (87.4% vs. 82.3%) compared to CEUS LI-RADS.
Conclusion: Kupffer phase defect could improve sensitivity for HCC diagnosis than late and mild washout and applying Kupffer phase defect in LI-RADS could aid in enhancing the diagnostic value.

FRI275

Impact of contrast-enhanced ultrasound on detection of colorectal liver metastases and therapeutic strategy in patients with newly diagnosed colorectal carcinoma after staging with computertomography. A prospective cohort study

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Background and Aims: Colorectal carcinoma (CRC) is the second leading cause of cancer mortality in the world and up to 25% of patients with CRC have liver metastases (CRLM) at initial diagnosis. Early detection of CRLM is important for prognosis and therapeutic strategies. Contrast-enhanced CT may miss up to 30% of liver metastases. The objective of this prospective study was twofold: first, to assess the impact of contrast-enhanced ultrasound (CEUS) on the detection rate of CRLM compared to standard staging-CT; and second, to evaluate the resulting impact of CEUS on changes of therapeutic strategies.
Method: We prospectively analysed all patients with newly diagnosed CRC at our tertiary gastroenterological centre between December 2015 and May 2019. All patients with newly diagnosed

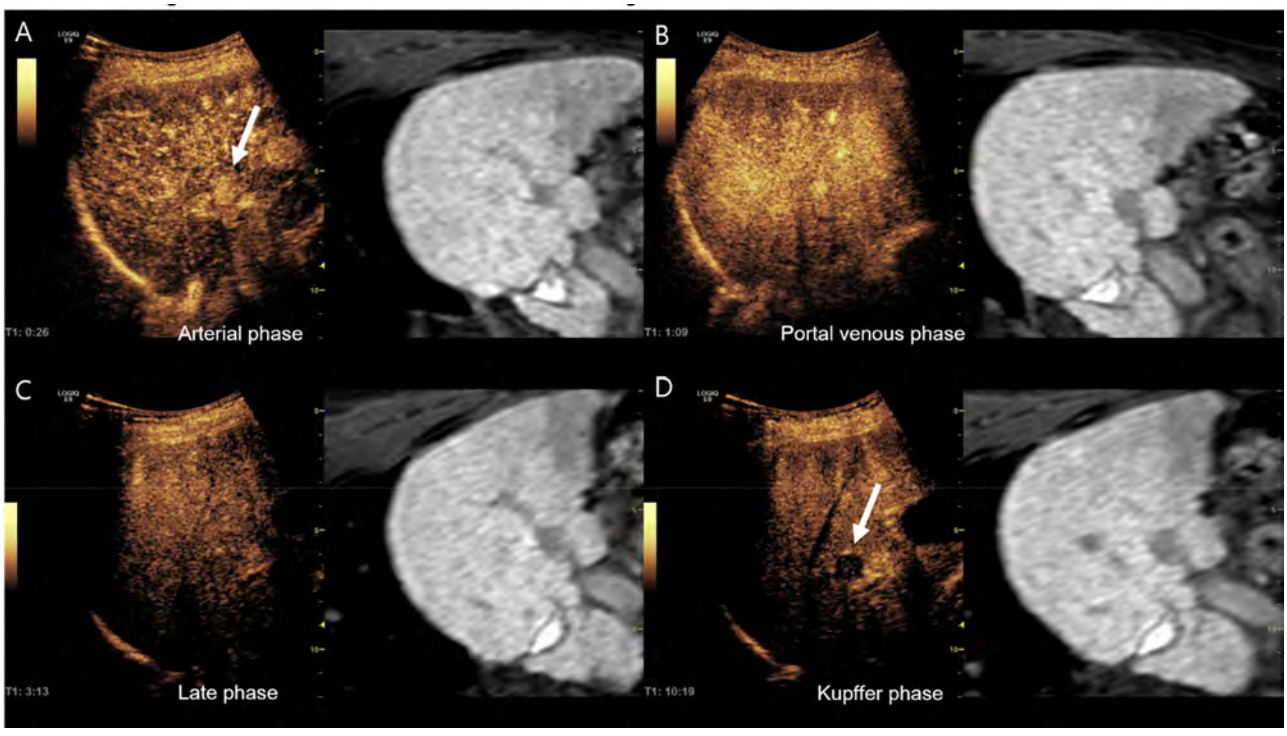

Figure: (abstract: FRI274): Sonazoid®-enhanced US with imaging fusion technique for CT/MRI LI-RADS LR-5 nodule in a 68-year-old woman with chronic viral hepatitis B. (A) Arterial phase image shows about 1.2 cm hyperenhancing liver nodule (arrow) in hepatic segment VII. (B-C) Portal venous and late phase images show no late and mild washout. (D) There is Kupffer phase defect (arrow). The liver nodule was assigned LR-5 according to modified CEUS, but LR-4 according to CEUS LI-RADS.

CRC by colonoscopy and histology without CRLM or with unclear (benign or malignant) focal liver lesions in CT were recruited. CEUS was performed by a single experienced hepatologist to avoid interobserver variation using renal-independent 0.8 to 1.5 ml intravenous contrast agent (SonoVue ®) with intermittent ultrasound scanning up to 5 minutes. Standard of reference (SOR) was obtained by MRI or histology (if CRLM was detected).

Results: We enrolled prospectively 296 patients (median age of 68 years) into this study. Eight additional CRLM were detected by CEUS (2.7%). CT had misdiagnosed these CRLM as hemangioma or as unclear focal liver lesions. The number needed to screen to detect one additional CRLM by CEUS was 37 patients. When results were reviewed by a board certified radiologist and oncologist, the therapeutic strategy changed in 6 of these 8 patients. All patients with CRLM detected by CEUS only were staged pT3 or pT4 CRCs. Among the 58 patients with focal liver lesion (FLL) of unknown dignity after CT, CEUS demonstrated benign FLL (hemangioma, cyst, focal liver (non)-steatosis and focal nodular hyperplasia) within 5 minutes in 90% of the patients.

Conclusion: In this study, CEUS detected 2.7% additional CRLM with a significant impact on the oncological therapeutic strategy for 75% (6/8) of these patients. Given a number needed to screen of 37 patients, CEUS may be cost-effective. Especially patients with CRC stage pT3 or pT4 seem to benefit from additional CEUS. Focal liver lesions of uncertain dignity after CT staging were determined as benign by CEUS in 90% of the cases.

Overall, CEUS appears to be a valuable and cost-effective diagnostic tool in patients with newly diagnosed CRC.

Rare liver diseases (including pediatric and genetic)

FRI276

The phenotype of compound heterozygous BSEP deficiency patients is determined by the combined residual function of the two ABCB11 mutations: results from the NAPPED consortium

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Background and Aims: Bile Salt Export Pump deficiency (BSEP-def), caused by mutations in *ABCB11*, frequently leads to end-stage liver disease and need for liver transplantation. Patients with homozygous (HO) p.D482G or p.E297G mutations have a relatively mild phenotype

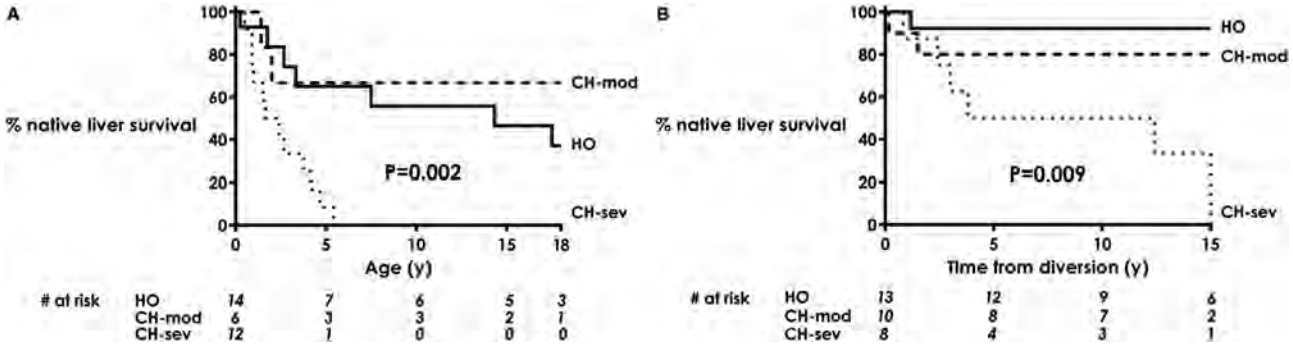

Figure: (abstract: FRI276): A: Native liver survival in patients with a homozygous (HO, solid line), compound heterozygous moderate (CH-mod, dashed line) or compound heterozygous severe (CH-sev, dotted line) genotype, without surgical biliary diversion. B: Native liver survival after surgical biliary diversion in patients with a homozygous (HO, solid line), compound heterozygous moderate (CH-mod, dashed line) or compound heterozygous severe (CH-sev, dotted line) genotype. Log-rank tests.

(Hep 2019;70:S1,48A). Serum bile acid (sBA) levels after surgical biliary diversion (SBD) allow prediction of subsequent survival with native liver (NLS, J Hep 2019;70:S1, e121). We aim to further specify genotype-phenotype relationships in compound heterozygous (CH) patients with one p.D482G or p.E297G mutation.

Method: From our global database we selected all HO p.D482G or p.E297G patients (n = 28) and CH patients in which one mutation was either p.D482G or p.E297G (n = 41). CH patients were further subdivided into two groups according to predicted genotypic severity: moderate (CH-mod; missense mutation, not p.D482G/p.E297G; n = 18) and severe (CH-sev; non-functional protein; n = 23). We compared biochemistry, SBD, post-SBD sBA levels and NLS. Continuous variables are expressed as median [IQR]. Appropriate non-parametric tests and log-rank tests were used.

Results: At presentation (median age < 1 y), liver tests were elevated, most pronounced in the CH-sev group (AST: 425 [170–762] IU/L in CH-sev; 218 [68–359] in HO; 169 [96–249] in CH-mod; P = 0.02). The groups did not differ in proportion of patients undergoing SBD (at age 5 y: 44–60%, P = 0.69). In patients without SBD, NLS was lowest in patients with a CH-sev genotype (NLS at age 15 y: 0% vs. 56% in HO and 67% in CH-mod; P = 0.002, Fig A). Post-SBD sBA levels were associated with NLS (NLS at 15y post-SBD: 95% at sBA <102 uM vs. 40% at ≥102 uM). The percentage of patients that obtained a post-SBD sBA <102 uM correlated with the severity of the second mutation (17% in CH-sev; 60% in CH-mod; 93% in HO; P = 0.001). NLS after SBD was markedly lower in CH-sev patients (NLS 15y post-SBD: 33% in CH-sev; 80% in CH-mod; 94% in HO; P = 0.004, Fig B). Mortality was comparable (0–7%, P = 0.25).

Conclusion: We were able to specify genotype/phenotype relationships in patients with compound heterozygous p.D482G or p.E297G *ABCB11* mutations. The severity of mutation on the second allele impacts the phenotype with regard to native liver survival and chance on long-term benefit of biliary diversion. Here we show, for the first time, that both alleles contribute and that the predicted total amount of residual function is critical to the phenotype.

FRI277

Proteostasis improvement in cystic cholangiocytes alleviates endoplasmic reticulum stress and halts polycystic liver disease

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Background and Aims: Polycystic liver disease (PLD) is a group of genetic disorders characterized by bile duct dilatation and/or progressive development of multiple intrahepatic biliary cysts (>10), which are the main cause of morbidity. Current surgical and/or pharmacological therapies exert modest benefits, and thus liver transplantation represents the only curative option. Recently, novel PLD-causative genes, encoding for endoplasmic reticulum (ER)-resident proteins involved in protein biogenesis and transport, were identified. Here, we hypothesized that PLD arises as a consequence of aberrant proteostasis in cystic cholangiocytes, representing a potential target for therapy.

Method: ER stress was assessed at transcriptional (qPCR), proteomic (mass spectrometry), morphological (transmission electron microscopy; TEM) and functional (20S proteasome activity) levels in different models of PLD (i.e., human and rat). Moreover, PCK rat (animal model of PLD) was employed to determine the effects of the ER stress inhibitor 4-phenylbutyric acid (4-PBA) and/or inducer tunicamycin (TM), in the progression of the disease. The impact of the aforementioned ER stress modulators was also analyzed on the expression of unfolded protein response (UPR) factors, the 20S proteasome activity, the mechanisms involved in the maintenance of ER proteostasis and the cell fate decisions (i.e., survival/apoptosis).

Results: The expression levels of the UPR factors were markedly upregulated in liver tissue from PLD patients and PCK rats, as well as in primary cultures of human and rat cystic cholangiocytes, compared to normal controls. Cystic cholangiocytes showed altered proteomic profiles, mainly related to proteostasis (i.e., synthesis, folding, trafficking and degradation of proteins), marked enlargement of the ER lumen (by TEM), and hyperactivation of the 20S proteasome. Notably, chronic treatment of PCK rats with 4-PBA decreased liver weight, as well as both liver and cystic volumes, of animals under baseline or TM administration compared to control groups. *In vitro*, 4-PBA downregulated the expression (mRNA) of UPR effectors, normalized proteomic profiles related to protein synthesis, folding, trafficking and degradation, and reduced the proteasome hyperactivity in cystic cholangiocytes, reducing their hyperproliferation and apoptosis.

Conclusion: Restoration of proteostasis in cystic cholangiocytes with 4-PBA halts hepatic cystogenesis, emerging as a novel therapeutic strategy.

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Persistently low platelet count and splenomegaly after treatment with oxaliplatin as markers of development of portal sinusoidal vascular disease

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Background and Aims: Oxaliplatin (OX) the most widely chemotherapeutic agent used in neo and adjuvant colon cancer (CRC), has been described as a potential etiologic agent for portosinusoidal vascular disease (PSVD). We aimed to describe the natural history of PSVD associated to OX (PSVD-OX) and identify risk factors for development.
Method: Multicenter, retrospective case-control study with patients diagnosed of PSVD-OX included in REHEVASC registry, with a history of exposure to OX and CRC. Baseline data (B), end of treatment (END-OX), years of follow up and end of follow up/diagnosis PSVD (F-PSVD) were collected and compared to 1.3 ratio controls (CRC without PSVD), matched by baseline characteristics, OX-dose and time of follow up.
Results: 41 cases were identified with a mean age of 56.6 ± 10.2 years, male sex 53.7%, rectum-sigma location (58.5%), liver metastases (26.8%), OX dose (median,range) = 1364.5 mg (705–17784 mg), anti-angiogenic agents (14.6%). The mean time to PSVD diagnosis after the end of OX was 33.7 ± 26.9 months, mostly asymptomatic, while 31.7% had complications of portal hypertension as first manifestation.15 patients presented gastrointestinal bleeding, 14 ascites and 9 thrombosis portal. In cases, platelet count (PLT) was markedly decreased from B to END-OX ($\times 10^9$/L): 269 ± 104 vs 120 ± 46; p = 0.0001 not recovering during follow-up and F-PSVD (269 ± 105 vs 102 ± 36; p = 0.0001). The 123 controls, PLT decrease was significantly lower and recovered during follow-up: B vs END-OX vs F-PSVD (274 ± 84 vs.142 ± 64, vs. 188 ± 73, p < 0.0001). At the first year post-OX, 29% of cases had <100 × 10^9 PTL vs 5% of controls (p < 0.001). Delta-PLT at END-OX and first year was significantly higher in cases (-149 ± 96 vs – 132 ± 93 × 10^9/L, p < 0.0001) and kept falling until F-EVPS Delta – 16 ± 6 × 10^9/L, while increased in controls +54 ± 71 × 10^9/L, p = 0.0001. Splenic longitudinal diameter (SLD) increased in cases respect B to END-OX and F-PSVD (cm) (10.7 ± 1.8 vs.12.8 ± 2.3 vs.14.8 ± 2.6; p <0.0001) and higher (p <0.001) than control group (END-OX 9.5 ± 1.5 and F-PSVD 9.8 ± 2.7, p < 0.001). Regarding markers of risk of PSVD development, SLD was the only variable that significantly persisted throughout the follow-up (multivariate analysis OR 0.596 (0.449–0.790); p < 0.0001), while PLT was only significant at END-OX OR 1.008 (1.000–1.016) p = 0.05. The increase in SLD was the strongest predictor of PSVD during treatment OR 43.94 (14.48–133.336) p < 0.0001, and Delta-SLD > 3.1 cm, at the first year post-OX had an AUROC = 0.855 S = 0,99 and E = 0.67, (p < 0.001) for PSVD; while Delta-PLT>-202 × 10^9, the AUROC = 0.653 with S = 0.92 E = 0.75 p < 0.007.
Conclusion: Low platelet count and the increase in SLD maintained after OX can be considered risk factors for PSVD and therefore, these patients could be candidates for a specific follow-up of portal hypertension complications.

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Cross-talk between regulation of iron homeostasis and gluconeogenesis in a murine model of hereditary hemochromatosis

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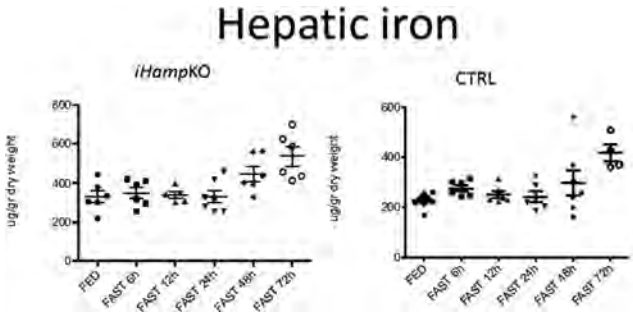
Background and Aims: The relationship between glucose homeostasis and iron metabolism has been increasingly studied over recent years. We have previously shown that hepcidin, the iron-hormone defective in hereditary hemochromatosis (HH), is up-regulated by glucogenic signals and its target-receptor, ferroportin, down-regulated, thus leading to liver iron overload and suggesting a defensive response, led by hepcidin, to metabolic stress. Since patients with HH may present diabetes and metabolic alterations, we wondered whether hepcidin deficiency per se might represent a pathogenic co-factor. We therefore studied adaptation to starvation, a model for insulin-resistance and activated gluconeogenesis, in murine HH.
Method: Eight to 10-week-old male conditional Hamp-/- (iHampKO) or control (CTRL) mice were first i.p. injected with tamoxifen, to induce hepcidin gene deletion in iHampKO, and then starved up to 72 hours or fed a standard diet. Biochemical, nutritional, serum and tissue iron parameters were determined. The expression of genes involved in iron metabolism and gluconeogenic response was assessed by qRT-PCR and western-blot analysis
Results: Starvation induced gluconeogenic genes Pepck and Pgc1a in CTRL mice, but such increase was delayed and less prominent in iHampKO mice. Mortality was not significantly different between groups. Serum glucose decreased gradually and equally in both iHampKO and CTRL mice with progression of starvation (p < 0.0001). In iHampKO mice serum iron decreased during starvation (p < 0.0001) whereas, in spite of hepcidin deficiency and consequent ferroportin up-regulation, hepatic iron progressively increased as compared to fed iHampKO mice, particularly at 72 hours (starved vs fed mice, p = 0.005), similarly to CTRL mice. Such hepatic iron accumulation was not due to upregulation of iron importers, as confirmed by unchanged levels of Tfr1 and Zip 14 mRNA expression and/or protein.



Conclusion: In murine HH, gluconeogenic gene response is partly blunted but preserved, and metabolic compensation or overall survival are not negatively affected. This indicates that hepcidin deficiency per se in HH does not impair metabolic adaptation.

Interestingly, hepatic iron overload during starvation seems due to iron retention, independent on the hepcidin-ferroportin axis,likely aimed at preserving iron for vital energetic functions. Studies are ongoing to dissect the molecular basis for this novel regulatory pathway.

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Custom-designed next generation sequencing panel for genotype identification in cholestasis

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Background and Aims: Inherited cholestatic liver diseases of varying severity were linked to genetic variants in ATP8B1 (FIC1), ABCB11 (BSEP), and ABCB4 (MDR3) in the late nineties. Moreover, using next generation sequencing (NGS) techniques, genetic variants in further genes, such as NR1H4 (FXR), TJP2, and MYO5B were identified as molecular basis for intrahepatic cholestasis of varying severity. Genetic analysis represents an important tool not only to confirm clinical diagnosis but also for individual surveillance strategies and targeted therapeutic approaches.
Method: We created a custom-designed NGS panel comprising coding sequences and flanking intronic regions of more than 30 genes and over 16 specific hot spot regions. The panel includes genes known to be related to mono- and polygenetic cholestatic liver diseases as well as possible candidate genes involved in hepatobiliary transport and therefore cholestasis. The hot spots comprise specific genetic variants, which may affect progression of liver diseases acting as disease modifiers.
Results: Over 300 NGS analyses were performed for patients with intrahepatic cholestasis and a suspected genetic contribution. More than 100 different potentially pathogenic variants were detected in the cholestasis-associated genes ATP8B1, ABCB11, ABCB4, NR1H4, TJP2 and MYO5B including 18 novel variants. About one third of the analysed patients revealed at least two heterozygous variants in different cholestasis-associated genes suggesting that this complex genotype may be sufficient to elicit a cholestatic phenotype besides homozygous or compound heterozygous variants in one gene. Moreover, variants in TJP2 and MYO5B may also result in milder forms of cholestasis such as a benign recurrent intrahepatic cholestasis (BRIC)-like phenotype as described for ATP8B1 and ABCB11.
Conclusion: We created a custom-designed NGS panel to determine the genetic contribution in patients with cholestatic disorders. NGS analysis of cholestasis-associated genes underscores that multiple variants in different cholestasis-associated genes may cause a cholestatic phenotype. Furthermore, milder forms of cholestasis like BRIC may also be related to genetic variants in TJP2 and MYO5B.

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ABCB4/MDR3 gene mutations in young patients with symptomatic cholelithiasis

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Background and Aims: Low phospholipid-associated cholestasis and cholelithiasis syndrome (LPAC) is characterized by recurrent symptomatic cholelithiasis in young adults and is associated with mutations of the *ABCB4/MDR3* gene. The **primary aim** of our study was to evaluate the prevalence of ABCB4/MDR3 mutations in patients with symptomatic cholelithiasis before 30 years of age.
Method: We conducted an interim analysis of a prospective study, since January 1, 2017, including patients with symptomatic cholelithiasis before 30 years of age from 4 Portuguese centers. Patients' clinic and demographic data was collected, and *ABCB4/MDR3* gene was analyzed by next generation sequencing including all exons and flanking regions. In addition, other intra-hepatic cholestasis associated genes (*ABCB11, ATP8B1*) were also analyzed in one center.
Results: We have included 30 patients, 23 of them women, mean age 28 ± 8 years (min 13, max 49). Mean age of symptoms onset was 23 ± 4 (min 11, max 30). Most frequent clinical presentation was biliary colic (n = 10), followed by choledocholithiasis (n = 8) and acute cholecystitis (n = 5). Seven patients had family history of biliary symptoms (1st degree relatives). Twenty-three patients were submitted to cholecystectomy, and thirteen (57%) had symptoms/complications recurrence after surgery. Two patients had liver echogenic foci suggestive of intrahepatic lithiasis or sludge in abdominal imaging. Eighteen (60%) patients met clinical criteria for LPAC syndrome – 7 of them (39%) had *ABCB4* mutations (2 in homozygosity, 4 in combined heterozygosity, 1 single *ABCB4* heterozygous missense variant) and 1 had a single heterozygous missense variant in the *ABCB11* gene. Of the 12 patients who didn't meet clinical criteria for LPAC syndrome – 1 had a single *ABCB4* heterozygous missense variant and 3 had missense variants in the *ATP8B1* gene (1 in homozygosity and 2 in heterozygosity). Fourteen patients had other risk factors for cholelithiasis (obesity, combined oral contraceptives, postpartum, dyslipidemia, diabetes) – 3 (21%) of them had gene mutations (2 in *ABCB4* and 1 in *ATP8B1*). We found a tendency for association of 1st degree relative family history and ABCB4 mutation (p = 0,06), in fact 3 patient relatives tested positive for the same mutation. Overall prevalence of ABCB4 gene mutations was 27% (8/30) and of cholestasis related gene mutations was 47% (8/17). Eleven patients were put on ursodeoxycholic acid (8–15 mg/Kg/day) and had no symptom recurrence since. Median follow up time was 25 months.
Conclusion: We found a high prevalence of mutations in *ABCB4/MDR3* and cholestasis associated genes in general in patients with symptomatic cholelithiasis before 30 years of age – 27% and 47%, respectively. This highlights the importance of these entities, often underdiagnosed and with available and effective therapy to prevent complications in these patients.

FRI282

Efficacy of zinc on human hepatic copper uptake depending on zinc type and dose regimen quantified with 64-CuCl2 PET/CTscan

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Background and Aims: Zinc is used in the treatment of Wilson's disease (WD) and works by blocking intestinal copper uptake. Current recommended dose is 50 mg thrice daily with a one hour fast before and after. Different types of zinc salts exist but only one, zinc acetate (Zn-ac), is approved as treatment of WD. Our aim was to investigate the effect of different zinc types and dose regimens on hepatic copper uptake.
Method: In an interim analysis, we included the first 15 healthy individuals in a randomized, non-blinded clinical trial. Hepatic copper uptake was determined with 64-Cu PET/CT scans before and after four weeks of treatment with either Zn-ac 50 mg × 3 daily, Zn-ac 150 mg × 1 daily or zinc gluconate (Zn-glu) 150 mg × 1 daily. The effect was quantified as the relative difference in mean standard uptake value in the liver.
Results: The effect on copper uptake varied substantially among the individuals, and 3/15 participants had no effect. The mean ratio was

0.39 (SD: 0.19) for Zn-ac 50 mg × 3, 0.60 (SD: 0.35) for Zn-ac 150 mg × 1, and 0.90 (SD: 0.23) for Zn-glu 150 mg × 1, indicating that all treatments lowered hepatic copper uptake. There was no significant difference in the effect on copper uptake between Zn-ac thrice or once daily (p = 0.26), or between Zn-ac and Zn-glu once daily (p = 0.15). There was a difference between Zn-ac thrice and Zn-glu once daily (p < 0.05).
Conclusion: The effect of zinc treatment on hepatic copper uptake is highly variable but quantifiable by 64-Cu PET/CT scan, indicating that efficacy evaluation by 64 Cu-PET/CT is advisable in WD. Zinc thrice daily was not significantly different than once daily as long as the zinc type was Zn-ac.

FRI283
High burden of future liver disease in intrahepatic cholestasis of pregnancy patients
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Background and Aims: Intrahepatic cholestasis of pregnancy (ICP) occurs in 0.3% of all pregnancies and may be linked to future liver disease. There are currently no guidelines for liver follow up care for women with ICP. Using a cohort of women with ICP and controls, we investigated incidence, predictors, and time to future liver disease.
Method: We conducted a retrospective cohort study of pregnant women with and without ICP who delivered between 2005–2009 at a community hospital in New York City with a high prevalence of ICP (2.5% of all deliveries). Women returning for care with liver function tests at a minimum 6 months post-partum were included in the analyses. We examined prevalence and time to the development of two outcomes: (1) ALT > 25 U/L (the upper limit of normal) and (2) diagnosis of liver disease (through imaging or clinical evaluation). Analyses were performed using Kaplan Meier methods and we fit Cox regression models.
Results: We identified 255 women with ICP and 100 control patients who returned to care within the study period. Subjects in both groups were similar in median follow up time, median age at time of pregnancy, median pre-pregnancy body mass index (BMI) and 80% or more of women in both groups identified as Hispanic.
Adjusting for metabolic factors including ICP diagnosis, ethnicity, diabetes status, BMI, maternal age, ICP diagnosis and class A2 gestational diabetes (GDMA2) diagnosis are associated with increased incidence of ALT > 25 U/L postpartum (HR 2.7, p < 0.0001 & HR 1.6, p = 0.02). For ICP and control women with ALT > 25 U/L, the median time to ALT > 25 U/L was 4.4 & 11.9 years respectively (p < 0.0001).
60 (24%) ICP patients and 19 (19%) controls were diagnosed with liver disease, the most common disease diagnosis being NAFLD. Adjusting for metabolic factors listed above, ICP is associated 1.8 times increased incidence of liver disease (p = 0.031), advanced maternal age is associated with 2.0 times increased incidence (p = 0.026), and Hispanic ethnicity is associated with decreased incidence of liver disease (HR 0.61, p = 0.032).
Conclusion: ICP diagnosis was found to be an important predictor of risk of future liver disease and abnormal liver tests. Women with pregnancies complicated by ICP, particularly those with GDMA2, and older than 35 at the time of ICP diagnosis could possibly benefit from surveillance for post-partum liver disease.

FRI284
Impact of nitisinone treatment and discontinuation on the metabolome of wild type and hereditary tyrosinemia type 1 mice
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Background and Aims: Hereditary tyrosinemia type 1 (HT1) patients are unable to fully break down L-tyrosine due to a deficient fumarylacetoacetate hydrolase (FAH) enzyme. Consequently, they suffer from a chronic loss of hepatocytes leading to cirrhosis and hepatocellular carcinoma. Nowadays, most patients are treated with the drug nitisinone that installs a metabolic roadblock by inhibiting the 4-hydroxyphenylpyruvate dioxygenase (HPD) enzyme upstream of FAH. In this study, we investigated the impact of nitisinone treatment and discontinuation on the serum metabolome of healthy wildtype (WT) and Fah-deficient mice by untargeted metabolomics.
Method: Fah^{5981SB} mice bear a single point mutation in the FAH gene, leading to an inactive protein that degrades. Serum was collected from Fah^{5981SB} and WT mice that received drinking water ad libitum supplemented with 8 mg/L nitisinone and from mice that were discontinued from nitisinone for seven consecutive days. Serum from untreated WT served as healthy control. On these samples, unbiased small molecule profiling was performed by high-resolution mass spectrometry using an Agilent 6550 QTOF-MS. Peak alignment, data normalization, compound identification and statistical analyses were performed using Progenesis QI software.

Table 1: (abstract: FRI283): Results of the Cox proportional hazards regression model

	Time to Liver disease				Time to ALT> 25 U/L		
Covariates	Hazard Ratio	95% CI	p value		Hazard Ratio	95% CI	p value
Hispanic ethnicity	0.61	0.39, 0.96	**0.032**		0.93	0.81, 1.1	0.25
Advanced Maternal Age (≥35 years)	2.0	1.1, 3.7	**0.026**		1.2	0.80, 1.8	0.40
GDMA2 diagnosis in current pregnancy	1.6	0.76, 3.3	0.22		1.6	1.1, 2.6	**0.02**
Overweight or higher (BMI >25 kg/m^2)	1.5	0.91, 2.5	0.11		1.1	0.81, 1.4	0.61
ICP diagnosis in current pregnancy	1.8	1.1, 3.2	**0.031**		2.7	1.9, 4.0	**<.0001**

Results: Treating healthy WT mice with nitisinone resulted in the accumulation of alternative tyrosine metabolites including acetyl-L-tyrosine, 4-hydroxyphenyllactic acid, 4-hydroxyphenylacetic acid and 4-hydroxybenzaldehyde. Conversely, key L-tryptophan metabolites of the kynurenine pathway were found to be decreased upon nitisinone treatment including kynurenine and picolinic acid. These metabolic changes were reversed upon discontinuation of the treatment. In addition, kynurenine and picolinic acid concentrations were found to be 2-fold higher in nitisinone-treated Fah^{5981SB} versus WT mice. Upon discontinuation of nitisinone treatment in Fah^{5981SB} mice, serum levels of ophthalmic acid, a glutathione analogue, raised by 3-fold.

Conclusion: Our study reports for the first time that L-tryptophan-related kynurenine metabolism is deregulated by nitisinone. This suggests that, besides HPD, nitisinone also inhibits a key enzyme involved in kynurenine metabolism. In addition, we propose ophthalmic acid as a potential biomarker to monitor the level of oxidative stress in HT1 patients due to hepatic glutathione depletion when nitisinone treatment is insufficient or discontinued.

FRI285

Prognosis in persons with an HFE-mutation: population-based cohort study of 3,645 individuals

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Background and Aims: Mutations in the HFE gene can lead to hemochromatosis and cirrhosis and have been suggested to also increase the risk of extra-hepatic diseases, especially breast and colorectal cancer. Most previous studies in this field have been small. Here we investigated long-term outcomes of a large cohort of patients with the most common HFE mutations.

Method: We identified 3,645 patients with either a homozygous C282Y (68%) or a C282Y/H63D (32%) mutation from eight centers in Sweden between 1997 and 2017. These were matched 1:10 by age, sex and county of residence at the time of HFE testing to a reference population. We ascertained incident diagnoses until the end of 2017 by linkage to national registers on hospital-based care and prescribed drugs. Studied outcomes included hemochromatosis, cirrhosis, hepatocellular carcinoma (HCC), breast cancer (in women), colorectal cancer, type 1 and 2 diabetes, hypothyroidism, Parkinson's disease and overall mortality. Cox regression was used to estimate hazard ratios for the outcomes in patients with HFE mutations compared to the reference population.

Results: Median age at diagnosis was 52 years and 44% were females. During a follow-up of in mean 7.9 years, we found an increased risk for HCC, hemochromatosis, cirrhosis, type 2 diabetes, and death. No increased risk was seen for other outcomes (Table 1). Liver-related outcomes were rare, with a cumulative incidence of <1%.

Conclusion: In this large cohort study we found no increased risk for extra-hepatic malignancies in persons with verified HFE mutations.

Table 1: (abstract: FRI285)

Incident outcomes	N (%) HFE	N (%) controls	Incidence rate per 1000 person-years, cases with HFE (95%CI)	Incidence rate per 1000 person-years, controls (95%CI)	aHR	95%CI	P
HCC	23 (0.63)	12 (0.03)	0.80 (0.53, 1.21)	0.04 (0.02, 0.07)	21.32	10.34, 43.97	<0.01
Colorectal cancer	50 (1.37)	570 (1.57)	1.03 (0.71, 1.49)	1.05 (0.94, 1.18)	0.99	0.67, 1.46	0.97
Breast cancer	73 (2.00)	742 (2.04)	1.03 (0.71, 1.50)	0.95 (0.84, 1.07)	1.08	0.73, 1.60	0.68
Type 1 DM	6 (0.21)	79 (0.27)	0.18 (0.06, 0.56)	0.08 (0.04, 0.13)	2.34	0.67, 8.22	0.18
Type 2 DM	283 (9.82)	2293 (7.96)	7.57 (6.33, 9.05)	5.72 (5.37, 6.09)	1.36	1.12, 1.64	0.002
Hypothyroidism	278 (9.64)	2101 (7.29)	4.90 (3.92, 6.12)	3.92 (3.63, 4.23)	1.25	0.99, 1.58	0.06
Parkinson's disease	7 (0.21)	142 (0.42)	0.13 (0.04, 0.39)	0.37 (0.30, 0.45)	0.35	0.11, 1.10	0.07
Cirrhosis	13 (0.38)	60 (0.18)	0.38 (0.20, 0.73)	0.18 (0.13, 0.24)	2.15	1.05, 4.41	0.03
Hemochromatosis	1694 (49.7)	18 (0.05)	119.01 (113.11, 125.22)	0.04 (0.02, 0.08)	2317.90	1280.75, 4194.92	<0.01
Death	339 (9.30)	3149 (8.65)	12.29 (11.05,13.67)	11.01 (10.64, 11.41)	1.16	1.04, 1.30	0.009

FRI286

Cracking the notch code in alagille syndrome: single-cell receptor-ligand interactions and outcomes in vivo, and an emerging role of immune cells

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Background and Aims: Alagille syndrome (ALGS) is a dominant multi-systemic disorder caused by mutation of either the Notch ligand *JAGGED1* or the receptor *NOTCH2*. Impaired JAG1/NOTCH2 signaling leads to developmental defects in heart, bones, eyes, and liver, where it can lead to bile duct paucity (*1*). Notch signaling also regulates haematopoiesis and immune cell maturation (*3*), and immunological features add to the complexity of ALGS (*2*). However virtually nothing is known about the interaction between blood cells and biliary cells during bile duct maturation, when these systems are in immediate contact. Does the altered profile of immune cells in ALGS patients reflect an immune response to the biliary failure, modify the biliary phenotype, or represent a separate Notch-dependent phenotype? Notch receptors and ligands are expressed throughout the embryonic liver (*4*), in both liver cells and hematopoietic cells. However, the parameters dictating the output of Notch receptor-ligand interaction - the "Notch code" – remains poorly understood.
Method: We investigated the Notch code, and the interaction of the biliary and hematopoietic system, in $Jag1^{Ndr/Ndr}$ mice, which carry a homozygous $Jag1^{H268Q}$ mutation, and faithfully mimic ALGS (*5*). 10X Genomics scRNAseq of early postnatal (P3) $Jag1^{Ndr}$ liver was used to identify cell types and Notch component expression. To test Notch signalling parameters in a clean system, we generated "Notch-clean" reporter cells using CRISPR (*6*). Notch receptor-ligand output was assessed using these reporter cells, in combination with high-throughput live imaging.
Results: We generated cell lines devoid of either all 4 Notch receptors ($NOTCH1/2/3/4^{-/-}$), multiple Notch ligands ($JAG1/2^{-/-}$, $DLL4^{-/-}$, $DLL1/3^{-/in\ frame}$), or both ($NOTCH1/2/3^{-/-}$, $NOTCH4^{+/+}$, $JAG1/2^{-/-}$, $DLL1/3^{-/in\ frame}$, $DLL4^{+/-n}$). We designed a library of Notch ligands (JAGGED1/2, DELTA-LIKE1/3/4), and Notch receptors (NOTCH1-4) with permanent (EGFP, HA), or transient T2A fused fluorescent tags (EGFP, RFP670-N1). Together with our new fluorescent Notch reporter (12 × CSL-H2B-m1RFP-PEST), this allows non-disruptive quantification of Notch signaling in individual cells using live cell imaging.
Single cell analysis of >40,000 randomly sampled cells from control and $Jag1^{Ndr/Ndr}$ P3 livers revealed a preponderance of haematological cells at this stage in both control and $Jag1^{Ndr/Ndr}$ liver, but with further enriched numbers, and altered characteristics, of specific immune cells and their precursors, in the $Jag1^{Ndr/Ndr}$ liver.
Conclusion: Immunological dysregulation in ALGS is detectable shortly after birth in the mouse model. How this interacts with the biliary phenotype is currently under investigation. Together with our new Notch reporter assays, we now aim to unravel the signalling and developmental mechanisms controlled by biliary-hematopoietic system interaction. (Refs on poster.)

FRI287

Real-world disease burden, treatment patterns, and outcomes of hospitalized patients with hepatic encephalopathy

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Background and Aims: Hepatic encephalopathy (HE) is a serious clinical complication of cirrhosis and/or portosystemic shunting with a substantial economic burden. This study aimed to evaluate the characteristics of patients hospitalized with HE, treatment patterns, clinical outcomes, health care resource utilization (HCRU), and costs during hospitalization. It also evaluated readmission rates and mortality rates post-discharge.
Methods: This retrospective study using the nThrive Health System Data (US hospital encounter database from over 400 US hospitals) included adults with an incident inpatient HE diagnosis during 01FEB2014-30APR2018 (index hospitalization: the first inpatient stay with HE diagnosis) and a diagnosis for liver cirrhosis within 90 days prior to or during index hospitalization. Outcomes analyzed included comorbidities, medications, procedures, mortality rate, HCRU and costs during index hospitalization. It also analyzed readmission rate and mortality rate during 30 to 180 days after the discharge from index hospitalization. Standard summary statistics are presented for all outcomes.
Results: Among the 24,093 eligible patients (mean age: 59.1 years; 61.7% males), the most common comorbidities during the index hospitalization included cardiovascular disease (79.8%), electrolyte imbalance (61.0%), and acute/chronic kidney disease (50.7%). The most commonly used medications included lactulose and rifaximin (lactulose only: 45.5%; rifaximin only: 2.1%; combination: 30.0%). On average, patients had 1.1 procedure and a hospital stay of 8.1 days during the index hospitalization. The average total cost and charge of hospitalization was $18,297 ($2,180/day) and $79,439 ($9,538/day), respectively, with an 11.4% in-hospital mortality rate. During the 30 to 180 day period post-discharge from index hospitalization, there were increasing trends observed for all-cause readmission rate (16.5% to 34.7%), HE-related readmission rate (9.7% to 22.4%), and all-cause mortality rate (1.7% to 4.8%).
Conclusion: Results from this latest US hospital database study indicate that hospitalized HE patients have a substantial comorbidity burden with in-hospital mortality of 11.4%, length of stay of 8.1 days, and total in-hospital costs of $18,297. Increasing trends for mortality and readmission rates were also noted during 30 to 180 days post-discharge from the hospital. These findings underscore the need for new, more effective treatments to better control and manage HE.

FRI288

Liver ultrasonic transient elastometry (fibroscan (r)) in hepatic amyloidosis: results of a multicenter cohort of 26 cases

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Background and Aims: Transient elastometry (E) (Fibroscan®) is a physical method that measures the stiffness of liver fibrosis. It was validated by HAS for its evaluation in patients with chronic hepatitis C, without comorbidity and in other indications. The hepatic elastometric values may be also elevated in other situations i.e: acute hepatic cytolysis, cardiac liver failure, and cholestasis syndrome. During amyloidosis with liver injury, the liver is hard without correlation with the degree of fibrosis. The purpose of this study is to report the results of elastometry values during liver amyloidoidosis in a multicenter study.
Method: 26 patients with amyloidosis followed in 5 centers were included. All patients had an evaluation of their E by Fibroscan according to the manufacturer's recommendations with at least 10 measurements; only results with an IQR < 30% and a success rate (TR) > 60% are interpretable. The statistics are presented in median and quartile.
Results: 9 women and 17 men with 62 years old median age (Q25 = 68 years, Q75 = 72 years) were studied. 24 had AL amyloidosis. The result of elastometry made possible diagnosis of liver amyloidosis in 3 among 26 cases (12%) in patients with unknown liver disease. 18 patients had cardiac failure (69%), 16 had renal impairment (64%), 26 (100%) had liver injury: hepatomegaly n = 21 (81%); splenomegaly n

= 8 (31%); Unintentional weight loss n = 11 (42%). 11 (42%) had ventricular dysfunction and 4 (15%) had inferior vena cava dilatation. All patients had remarkable anicteric cholestasis (median = 2.2 times the upper limit of normal, Q25 = 1.6N, Q75 = 2.8N). Transaminases were normal in 25 of the 26 patients, the median serum creatinine was 83 μmol/L (Q25 = 75 μmol/L, Q75 = 109 μmol/L).
The median of elastometry was 48 kPa (Q25 = 17 kPa, Q75 = 75 kPa), 50% of patients had an IQR of 0% elastometry. The median value of the IQR was 0.5 points, (Q25 = 0 pt, Q75 = 17 pts).
Fibroscan was interpretable in 100% of patients without cardiac involvement with a median value of 27 kPa (Q25 = 13 kPa, Q75 = 75 kPa) and a median IQR of 0 points (Q25 = 0 pt, Q75 = 2.5 pts), in patients with cardiac involvement the median of fibroscan was 59 kPa (Q25 = 27 kPa, Q75 = 75 kPa) and a median IQR of 7 points (Q25 = 0 pt, Q75 = 20 pts). The difference in median elastometry if there was cardiac involvement was 11 kPa (p = 0.42) and a median IQR difference of 11 points (p = 0.03); 22% of patients with cardiac involvement had uninterpretable fibroscan. 9 patients performed a transjugular liver biopsy to confirm the diagnosis of amyloidosis without extensive fibrosis.
Conclusion: Fibroscan makes possible diagnosis of amyloidosis in case of liver disease of undetermined etiology, which avoids invasive transparietal biopsy. These results suggest that the elastometric score during liver amyloidosis with or without cardiac involvement is very high and the accuracy of its measurement is reduced in case of cardiac involvement.

FRI289
Directed protein evolution as a tool to innovate gene therapy for hereditary tyrosinemia type 1
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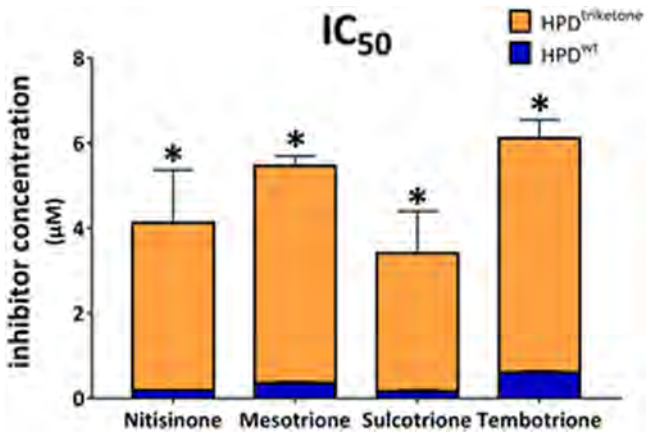
Background and Aims: Hereditary tyrosinemia type 1 (HT1) is a life-threatening hepatorenal disorder characterised by a dysfunctional fumarylacetoacetase (FAH) enzyme. HT1 can be effectively treated with the drug nitisinone (NTBC), a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase (HPD), an enzyme upstream of FAH. Gene therapy with the wildtype version of FAH would require withdrawal of NTBC due to the upstream metabolic block. Nonetheless, a low transduction efficiency impedes normalisation of the patient's metabolome and due to the cell-autonomous pathophysiology of the disease, withdrawal of NTBC is unacceptable. As a first step to solve the foregoing problem, we aimed to engineer an HPD enzyme with a significantly decreased sensitivity towards NTBC (HPD^{NTBC}) by the use of directed protein evolution technology.
Method: First, we developed a colorimetric bacterial whole-cell screening system that allows the evaluation of HPD variants in a high-throughput and a robust fashion ($Z' = 0.93 \pm 0.02$). The principle of the screening system is based on the degradation of tyrosine through 4-hydroxyphenylpyruvate into homogentisate by human HPD expressed in *E. coli* and subsequent production of a soluble melanin-like pigment. Next, the KnowVolution approach was used to engineer a human HPD enzyme with a significantly decreased sensitivity towards NTBC. This comprised the identification and determination of beneficial amino acid positions, substitutions and their recombination. Technologies that were used in iterative rounds of evolution included error prone (ep) PCR, site saturation mutagenesis (SSM) and site-directed mutagenesis (SDM).
Results: EpPCR allowed to identify 12 amino acid substitutions that decreased the sensitivity of human HPD towards NTBC. Combination of 8 out of 12 individual beneficial amino acid substitutions by SSM and SDM into a single lead variant further decreased the sensitivity of the engineered human HPD^{NTBC} enzyme towards NTBC as well as other triketone inhibitors. More specifically, the engineered lead variant exhibited significantly increased IC_{50} values versus wild type human HPD for the triketone inhibitors nitisinone (20.2-fold), mesotrione (14.1-fold), sulcotrione (19.8-fold) and tembotrione (9.0-fold) (Fig).



Conclusion: This NTBC insensitive human HPD variant comprises the first step in the development of new gene therapeutic approaches for the treatment of HT1 that are functional under NTBC treatment.

FRI290
Hospitalization rates of Budd Chiari syndrome in the United States
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Background and Aims: The current knowledge about the epidemiology of Budd Chiari Syndrome (BCS) in the United States is limited, and is based on data from case series and multi center studies that consisted of a relatively small number of patients. The primary objective of our study was to assess temporal trends in the prevalence of BCS among hospitalized patients in the US using the National Inpatient Sample (NIS) database and also to evaluate patient characteristics, risk factors and common presenting symptoms of BCS that required hospitalization. The NIS is the largest publicly available administrative database developed by AHRQ for the Health care cost and utilization project (HCUP) and represents approximately 20% stratified sample of discharges from the US hospitals.
Method: Data were extracted from the NIS to identify patients >18 years of age using all listed diagnosis (primary or secondary diagnosis) of BCS from 1998 to 2016. The diagnosis of BCS was captured using the codes 453.0 (ICD 9) and I82.0 (ICD 10).
Results: Between 1998 and 2016 we identified a total of 7,755 (unweighted) hospitalizations related to BCS and over the 18 year period, the hospitalization rate for BCS increased consistently from 4.96 per 1,000,000 US population in 1998 to 10 per 1,000,000 in 2016, with an annual percentage change (APC) increase of 4.25% (95% CI: 4.05% – 4.44%, $p < 0.0001$). Similarly, 5% increase was seen per 1,000,000 all cause hospitalizations (see figure). The mean age of the cohort was 50 years, 55.4% were female and 66.3% were white. The admission rate among Hispanics increased by 2.23% during this time period (p = 0.002). The underlying risk factors for BCS included myeloproliferative disorder (essential thrombocythemia or polycythemia vera) in 7.4%, a primary hypercoagulable state (protein C deficiency, factor 5 Leiden mutation, APLA or prothrombin gene mutation) in 6.8% and paroxysmal nocturnal hemoglobinuria in 1.7%. The most common manifestation of BCS among admitted patients

was ascites (30.2%) followed by acute kidney injury (18.1%). Other liver related complications of BCS included hepatic encephalopathy (9.3%), acute liver failure (5.4%), esophageal variceal bleeding (3.3%), IVC thrombosis (6.5%) and hepatorenal syndrome (3.3%).

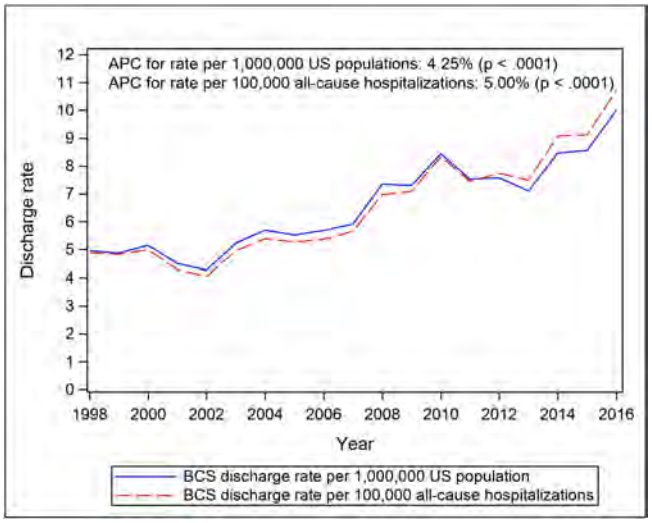

Figure: (abstract: FRI290)

Conclusion: This is the first and the largest population-based study in the United States to report increasing hospitalizations related to the Budd Chiari Syndrome.

FRI291

Health care burden and in-hospital mortality of BCS in the United States between 1998 and 2016

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Background and Aims: The Budd Chiari Syndrome (BCS) is a rare and potentially fatal disease, but there is a paucity of data on the in-hospital mortality of BCS as well its economic burden on the health care system. In this study, using a large administrative database we evaluated the trends in mortality, length of stay and resource utilization among inpatient with BCS.

Method: The NIS (National Inpatient Sample) is the largest publicly available administrative database developed by AHRQ for the Health care cost and utilization project (HCUP) and represents approximately 20% stratified sample of discharges from community hospitals. Data were extracted from the NIS to identify patients >18 years of age using all listed diagnosis (primary or secondary diagnosis) of BCS from 1998 to 2016. The diagnosis of BCS was captured using the codes 453.0 (ICD 9) and I82.0 (ICD 10).

Results: Between 1998 and 2016 we identified a total of 7,755 (unweighted) hospitalizations related to BCS. The overall in-hospital mortality rate among BCS patients decreased significantly by 5% ($p < 0.0001$) from 18% in 1998 to 7% in 2016, with the mortality rate being the lowest in 2015 (5%) (see figure). On multivariate analysis, older age, higher comorbidity score, acute liver failure, acute kidney injury, acute respiratory failure, IVC thrombosis and hepatorenal syndrome were associated increased risk of mortality. The average of length of stay for the cohort was 9 days and this consistently decreased by 2% ($p < 0.001$) from 13 days in 1998 to 8 days in 2016.

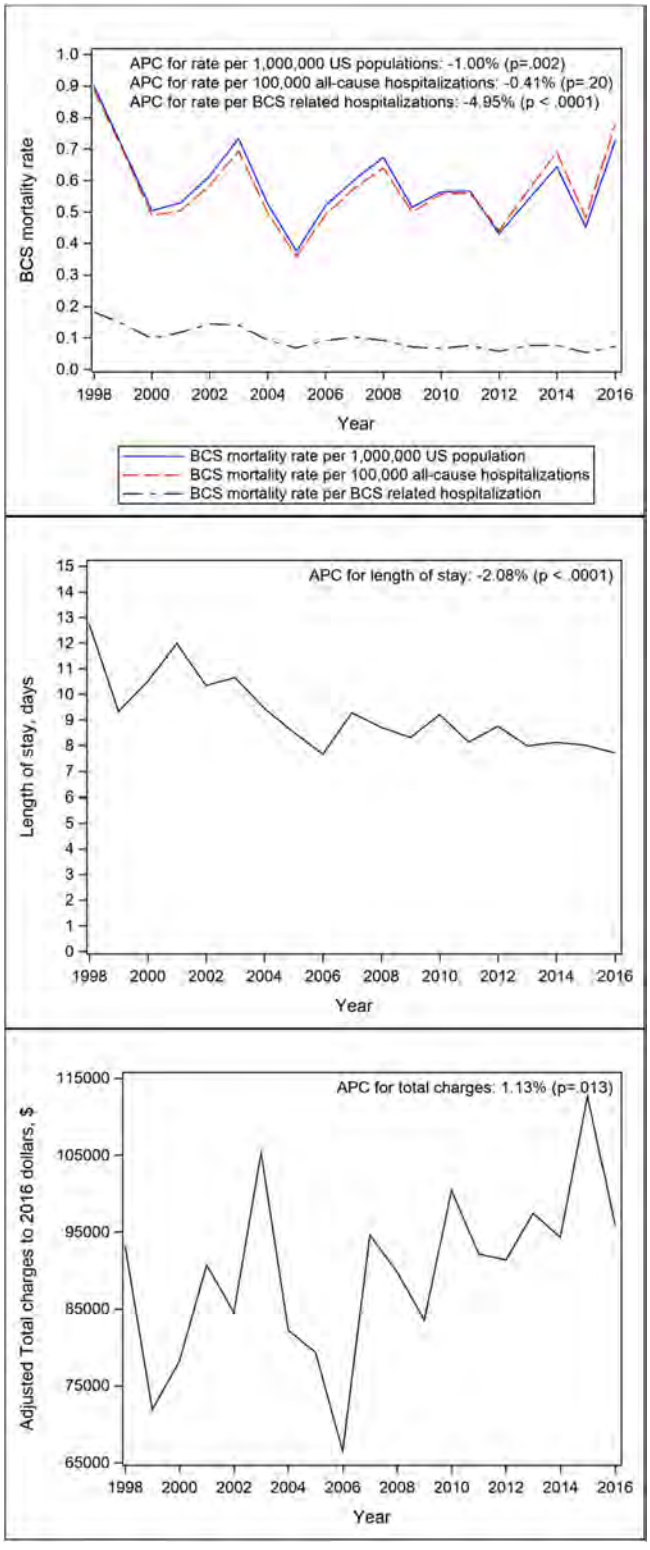

Figure: (abstract: FRI291):

During hospitalization, paracentesis was the most frequent procedure (18.6%) followed by upper endoscopy (10.7%), liver biopsy (6.3) and TIPS (3.7%). While total number of procedures performed remained stable during the study period, there was a significant and notable reduction in the number of liver biopsies (Annual

Percentage Change [APC]: −4.33%, P < 0.0001) and TIPS (APC: −5.41%, P < 0.0001).
The average total charges after adjusted for Medical Care Consumers Price Index to 2016 dollars during the time period was $91,280 and the annual percentage change (APC) increased by 1% (95% CI: [0.24%, 2.02%], p = 0.013) from $93,175 in 1998 to $95,822 in 2016. On multivariate analysis race, primary payer, number of procedures, length of stay, comorbidity score, hospital size, location and teaching status were associated with total charges. Important complications that had an effect on total charges included acute kidney injury, acute respiratory failure, IVC thrombosis and acute blood loss anemia.
Conclusion: The in-hospital mortality rate for patients admitted with BCS in the United States has reduced between 1998 and 2016. Despite the reduction in the length of hospital stay, total charges continue to rise.

FRI292

Genome-wide protective variants in MARC1 and HSD17B13 are associated with reduced inflammation and lower fibrosis stage on biopsy in children with NAFLD

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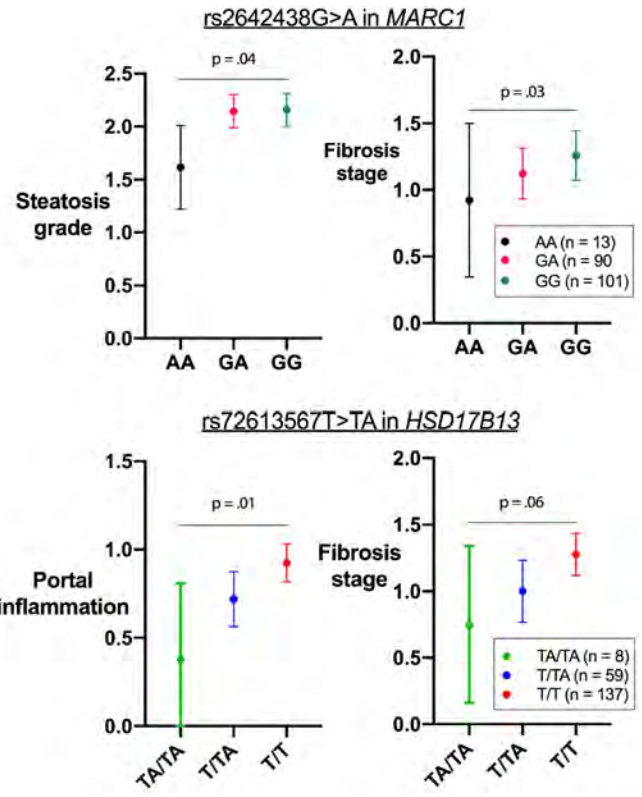
Background and Aims: Population-level coding data in adults has identified two common variants that are associated with protection against non-alcoholic fatty liver disease (NAFLD) and all-cause cirrhosis at genome-wide significance: rs72613567T > TA in HSD17B13 and, more recently, rs2642438G > A in MARC1. To date there is no histological data confirming the observation in MARC1 and neither have been studied in children. More generally, it is not entirely clear to what extent genetic influences are consistently shared in adults and children. Therefore we aimed to establish the effect these common variants had on histological features of NAFLD in children.
Method: Data from 204 children (<18 years) with biopsy-proven NAFLD were recruited from the European Paediatric NAFLD Registry and the Berlin paediatric NAFLD cohort. Histology was assessed according to the Non-Alcoholic Steatohepatitis Clinical Research Network scoring criteria. Participants were genotyped for rs72613567T > TA in HSD17B13 and rs2642438G > A in MARC1 using TaqMan genotyping. Expected genotype frequencies were tested using chi-squared analysis and histological differences between genotype were assessed using one-way ANOVA.
Results: The protective AA-genotype of rs2642438G > A in MARC1 was under-represented in this cohort compared to population prevalence (6% NAFLD vs. 9% population, p = .01). rs2642438G > A was associated with lower AST (p = 0.02), steatosis grade (p = 0.04), and fibrosis stage (p = 0.03).



The protective TA-allele of rs72613567T > TA in HSD17B13 was less prevalent in this cohort compared to population reference (18% NAFLD vs. 27% population, p = 0.002). The TA-allele was associated with lower portal inflammation (p = 0.01) and a trend towards lower fibrosis stage.

Conclusion: This is the first histological confirmation of the protective role of rs2642438G > A in *MARC1* in NAFLD, confirming the utility of coding data in identifying variants that influence NAFLD histology. Genome-wide significant protective variants have pervasive effects across adults and children, suggesting substantial genetic similarity between paediatric and adult NAFLD.

FRI293

Non-invasive screening for liver fibrosis by acoustic radiation force impulse in patients with ciliopathies

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Background and Aims: Ciliopathies are a heterogenous group of diseases caused by inherited malfunction of primary cilia. These antenna-like structures on the cell surface are involved in multiple signaling pathways and their dysfunction is most often associated with renal impairment but also (among others) retinitis pigmentosa, brain anomalies and hepatic fibrosis. The broad spectrum makes it difficult to predict liver involvement in individuals, yet knowledge is crucial for affected patients as advanced fibrosis may lead to variceal bleeding due to portal hypertension (PH). Acoustic radiation force impulse (ARFI) imaging is an ultrasound based elastography used for measuring tissue stiffness and thereby detecting fibrosis as well as PH. The aim of this study was to evaluate ARFI as a screening tool for liver involvement in ciliopathies in order to identify patients who are in need of treatment or may benefit from closer monitoring.

Methods: In a prospective cohort of 42 patients from the NEOCYST registry with ciliopathies (aged 1 – 74 years) stiffness of the right liver lobe and spleen was measured via ARFI and results were then compared with alanine transaminase (ALT) and platelets (the latter being a marker of PH) as well as histologic findings in 7 patients. All patients were clinically and n = 35 genetically diagnosed; most commonly with NPHP1, NPHP11 and HNF1B.
Results: ARFI-screening of the liver identified 26 patients without fibrotic conversion, 7 with moderate fibrosis (F1-F3) and 10 with severe fibrosis (F4), of which 6 had PH (Fig. 1). All 7 patients with histologically confirmed fibrosis were substantiated with decreased liver elasticity. In comparison to patients with normal elastography results, in ones with fibrosis the median ALT was significantly higher (40 ± 67 vs 106 ± 72 U/l, p = 0.008). Thrombocytopenia occurred more often in F4 patients. Yet some patients who showed increased liver stiffness had normal laboratory parameters (n = 3) and some patients with elevated ALT did not show increased liver stiffness (n = 3) (Fig. 1).

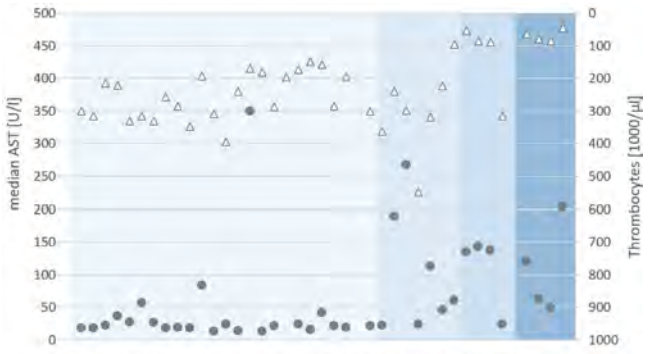

Figure 1: Platelet numbers (Δ) and median ALT values (•) visualized in ARFI-categories no fibrosis/F1-F3 fibrosis/F4 fibrosis without PH/F4 fibrosis with PH.

Conclusion: ARFI is an easy screening method that identifies a higher number of fibrotic patients than ALT and reliably identifies patients with severe PH. This study suggests integrating ARFI as a valuable non-invasive tool in evaluating patients with ciliopathies.

FRI294
Cholestatic phenotype of a mouse model for organic solute transporter? (OST?/SLC51B) deficiency suggest a role of the beta subunit beyond an OST? chaperone
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Background and Aims: The organic solute transporter alpha-beta (OSTalpha-OSTbeta) facilitates bile acid efflux mainly in ileal enterocytes, liver and kidney which is expected to protect cells from an overload of bile acids. OSTα-OSTβ consists of two distinct subunits expressed on separate genes. Heterodimerization is essential for transporter stability, trafficking to the plasma membrane and bile acid transport. OSTbeta deficiency in humans leads to congenital chronic diarrhea with features of cholestatic liver disease. In contrast, *Ostα*$^{-/-}$ mice displayed attenuated cholestasis-induced liver injury, by increasing urinary bile acid excretion. To elucidate the consequence of OSTβ deficiency in mice, we generated *Ostβ*$^{-/-}$ mice and compared them with *Ostα*$^{-/-}$ mice and wild-type littermate controls under standard and cholestatic conditions.
Method: *Ostβ*$^{-/-}$ mice were generated using the CRISPR/Cas9 system. Ileal organoids were isolated and cultured from *Ostβ*$^{-/-}$ and *Ostα*$^{-/-}$ mice, as well as their wild-type littermates. To induce cholestatic liver injury, mice were subjected to common bile duct ligation. Histological and biochemical parameters for liver damage were assessed.
Results: *Ostβ*$^{-/-}$ mice displayed a trend towards modestly elevated ALT and ALP levels, without other signs of cholestasis or diarrhea. Both *Ostα*$^{-/-}$ and *Ostβ*$^{-/-}$ mice exhibited longer, heavier small intestines and altered ileal histology, including blunted villi, increased crypt depth and increased mucus at the top of the villi. Increased gene expression levels of ileal *Fgf15*, and decreased *Asbt* expression, indicate accumulation of bile acids in the enterocyte. Organoids from *Ostα*$^{-/-}$ and *Ostβ*$^{-/-}$ cultured in the absence of bile acids show a similar phenotype and gene expression pattern as the wild-type organoids. Challenged by ligation of the common bile duct, clear differences between *Ostβ*$^{-/-}$ mice, *Ostα*$^{-/-}$ and wild-type mice were observed. All *Ostα*$^{-/-}$ and wild-type mice survived, with even a hepatoprotective phenotype in *Ostα*$^{-/-}$ mice, whereas 40–100% of the *Ostβ*$^{-/-}$ mice died within 5 days. Remarkably, a clear reduction was observed in plasma bilirubin (42%), cholesterol (38%) and bile acid levels (62%) in surviving *Ostβ*$^{-/-}$ mice. The *Ostβ*$^{-/-}$ mice that died did not produce feces, and display blackened content of small intestine and stomach.
Conclusion: OSTβ is a pivotal subunit for bile acid transport *in vivo* and its deficiency leads to an intestinal phenotype similar to *Ostα*$^{-/-}$ mice. Challenging *Ostβ*$^{-/-}$ mice by BDL reveals an unexpected phenotype, beyond the isolated hepatoprotection seen in *Ostα*$^{-/-}$ mice, suggesting that the chaperone function of OSTβ is not restricted to OSTα.

FRI295
Comparative pharmacokinetic profile of two distinct trientine salt formulations used for treatment of Wilson's disease
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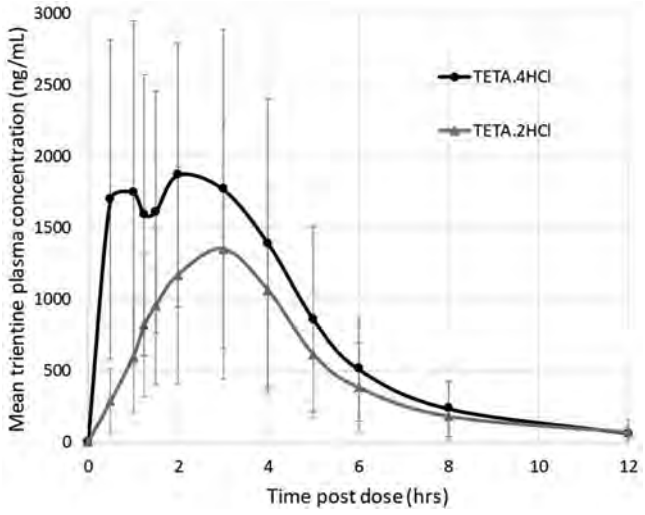
Background and Aims: Wilson disease is an autosomal recessive inherited disorder of copper metabolism requiring life-long medical treatment to control copper levels. The copper chelator Trientine Dihydrochloride (TETA.2HCl) is an established treatment for Wilson disease patients intolerant to D-penicillamine. A new salt Trientine Tetrahydrochloride (TETA.4HCl) has been recently approved in Europe (EU) for the treatment of Wilson disease. TETA.4HCl is stable at room temperature, while TETA.2HCl formulations require refrigerated storage. This study is the first to provide comparative pharmacokinetics (PK) on these two different oral Trientine salt formulations.
Method: In a randomised, cross-over study, 23 healthy adults received a single oral dose of TETA.4HCl tablets (gmp-orphan SA) and TETA.2HCl capsules (Univar BV). Blood samples were taken pre-dose and 0.5, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 30, 36, 42, 48 and 72 hours after dosing for analysis of plasma concentrations of Trientine and main metabolites using LC-MS/MS.
Results: Following the administration of a 600 milligram dose of active ingredient Trientine, there was significantly greater Trientine bioavailability with TETA.4HCl tablets versus (vs) TETA.2HCl capsules: Arithmetic mean (standard deviation, SD) for Cmax was 2340 (1170) vs 1490 (864) ng/mL and for AUC0-t was 10100 (5740) vs 6600 (3870) ng.hr/ml. Peak plasma levels were reached sooner with TETA.4HCl (median Tmax 2 vs 3 hrs). Arithmetic mean and SD of plasma levels of Trientine over first 12 hrs are shown in the figure.



Statistical comparisons of systemic Trientine exposure between the formulations following administration of the same oral dose gives the least square geometric mean ratios of 168 and 157 for Cmax and AUC0-t, giving an adjustment factor to the oral dose of approximately 0.6 (100/168 or 100/157) for comparable systemic exposure.
Conclusion: The recently approved TETA.4HCl salt provides a more rapid and extensive absorption of Trientine than the tested TETA.2HCl salt. A factor of approximately 0.6 can be applied to the oral trientine dose of the tested TETA.2HCl to provide comparable systemic exposure with TETA.4HCl.

FRI296

Differential expression of bile acid subspecies with maralixibat treatment in pruritus responders with bile salt export pump deficiency

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Background and Aims: Maralixibat (MRX), a nonabsorbable apical sodium-dependent bile acid (BA) transport inhibitor, interrupts the enterohepatic circulation of BAs and is proposed as a treatment for pediatric cholestasis and associated pruritus by reducing the accumulation of circulating and hepatic BAs. The open-label phase 2 INDIGO trial (NCT02057718) enrolled patients with progressive familial intrahepatic cholestasis due to bile salt export pump (BSEP) deficiency.
Method: In patients with mild to moderate nontruncating BSEP mutations (n = 19), MRX doses of 280 micrograms/kilogram/day, and later 560 micrograms/kilogram/day, were administered. Total and individual serum BAs (sBA), and 7 alpha-hydroxy-4-cholesten-3-one (sterol-C4), a marker of BA synthesis, were measured by stable-isotope dilution tandem mass spectrometry. Changes in the composition of sBA associated with pruritus improvement were investigated at week 72 in this ongoing trial in pruritus responders, defined as ≥1 reduction in the Itch Reported Outcome Observer (ItchRO[Obs]) score, compared with nonresponders.
Results: Of the 19 patients, 11 met the pruritus-response criteria, which correlated with the percentage reduction from baseline in total sBA and was significantly greater than in nonresponders ($p < 0.05$). Changes were also observed in the individual BA subspecies. Despite continued long-term therapy with ursodeoxycholic acid, reductions in glycine and taurine-conjugated cholic acid (TCA) were the best predictors of pruritus reduction due to MRX and correlated with percentage ItchRO(Obs) score reduction (Pearson correlation coefficient: 0.58, 0.50, 0.53 for TCA, glycocholic acid, and total cholic acid [CA], respectively). A trend towards increased proportion of unconjugated BA in responders (9.84 ± 4.87%) was observed compared with nonresponders (0.61 ± 0.24%, $p = 0.09$). Concomitant increases in serum sterol-C4 were observed in pruritus responders, consistent with the biological action of MRX.
Conclusion: Pruritus response with MRX in children with nontruncating BSEP deficiency was associated with BA composition changes. Reductions in serum CA conjugates, with concomitant increases in sterol-C4, were the best predictors of cholestasis and pruritus reduction associated with MRX treatment. These findings offer further interpretation on BA subspecies associated with reductions in cholestasis and pruritus with MRX.

FRI297

Clinical, histological, and biochemical liver phenotype of European adults with heterozygous alpha-1 antitrypsin deficiency (Pi*MZ genotype)

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Background and Aims: The 'Pi*Z' variant of alpha-1 antitrypsin (AAT) causes AAT retention within hepatocytes giving rise to globular inclusions and proteotoxic stress. While homozygous Pi*Z carriage ('Pi*ZZ' genotype) causes liver disease on its own, heterozygous carriage ('Pi*MZ' genotype) emerged as a strong genetic risk factor for cirrhosis in individuals with concomitant liver disease. As up to 4% of Caucasians are Pi*MZ carriers, our aim was to characterize the liver phenotype of Pi*MZ carriers without pre-existing liver disease.
Method: Our multinational, prospective cohort consisted of 421 Pi*MZ carriers, 309 Pi*ZZ carriers, and 284 non-carriers from 10 European countries. All underwent a comprehensive work-up as well as liver stiffness measurements (LSM) and controlled attenuation parameter (CAP) via transient elastography. Liver biopsies from 30 Pi*MZ and 35 Pi*ZZ individuals with signs of liver disease were used to define the histological and biochemical consequences of Pi*Z carriage. Data were adjusted for age, sex, BMI, diabetes mellitus, and alcohol consumption.
Results: Compared to homozygous Pi*ZZ subjects and Pi*Z non-carriers, heterozygous Pi*MZ participants had intermediate gamma-glutamyl transferase (GGT) and LSM values (all comparisons $P < 0.05$). 10% of Pi*MZ carriers vs. 4% of non-carriers had LSM ≥ 7.1 kPa (adjusted OR = 3.4 [1.6–7.3]). Age ≥ 50 years, male sex, obesity, presence of diabetes, and elevated GGT values associated with LSM ≥7.1 kPa in Pi*MZ carriers. No difference in CAP and metabolic parameters were detected between Pi*MZ carriers and non-carriers. On liver biopsies, AAT inclusions were detected in only 41% of Pi*MZ carriers (vs. 97% of Pi*ZZ carriers; Figure 1 A-B) and were more numerous in higher liver fibrosis stages (Figure 1 C-E). Accordingly, AAT genotyping was the only reliable method to diagnose Pi*MZ

status. Pi*MZ carriers did not harbor increased hepatic AAT levels, whereas the amounts of insoluble AAT displayed strong inter-individual variations.

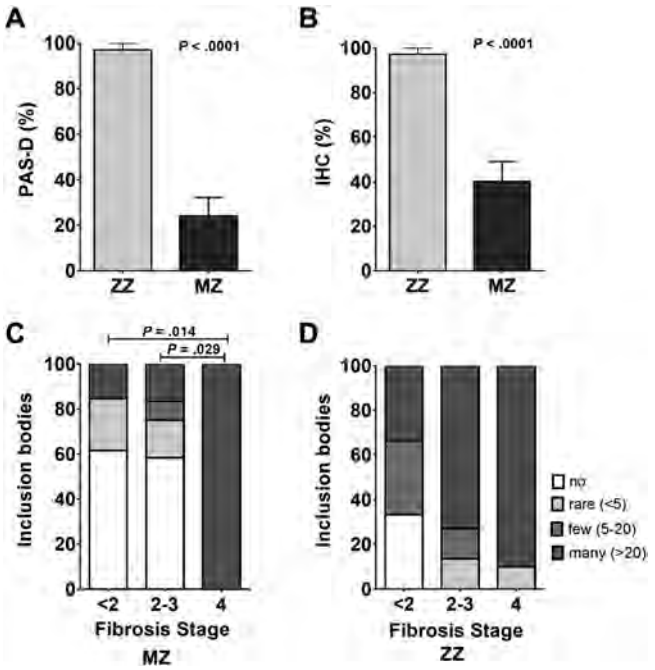

Figure: Histological features of Pi*MZ carriers vs. Pi*ZZ subjects. Histological analysis of liver biopsies from 30 Pi*MZ and 35 Pi*ZZ individuals with signs of liver disease. Rate of inclusion bodies seen on PAS-D staining (A) and immunohistochemistry (B) in Pi*ZZ (left) and Pi*MZ subjects (right). Rate of inclusion bodies depending on the fibrosis stage (as determined by the Kleiner classification) in Pi*MZ (C) and Pi*ZZ individuals (D).

Conclusion: This hitherto largest analysis of Pi*MZ carriers defines their clinical and biological consequences and demonstrates an intermediate clinical and histological liver phenotype compared to Pi*ZZ subjects and Pi*Z non-carriers. Our data should help in risk stratification and counseling of these individuals.

FRI298

Customized xenograft model development: liver repopulation of FRG® KO mice with primary hepatocytes from donors carrying specific genetic variants

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Background and Aims: Liver-humanized mice have proven to be of great use for in vivo studies in many application areas including infectious diseases, NAFLD/NASH, gene editing/therapy, metabolism, regenerative medicine, and pharmacology/toxicology.
The FRG KO mice can be repopulated with hepatocytes from different species.
Similarly, hepatocytes from donors with specific mutations of interest can be transplanted into the FRG mouse model to enable research of the human disease in human hepatocytes in vivo.
Method: FRG KO mice were transplanted with hepatocytes from various sources. These include different species: mouse, rat, pig, non-human primate, or human.
To compare the efficacy of different human donors to humanize the liver of FRG KO mice, we selected donors with a wide variety of age, BMI, genetic background, metabolic disease state.
Results: Using a standardized protocol, we were able to generate FRG KO mice that were highly repopulated with a xenograft liver. On average, it takes approximately 12 weeks to repopulate the animal's liver. The percentage of repopulation was consistently above 90%. Once repopulated, the xenograft remains stable for the remainder of the animal's life.
The liver-xenograft mice show a metabolism profile of the original donor species. This allows the testing of novel compounds in a small animal model.
Murinized FRG KO mice are used frequently as a control for liver-humanized FRG KO mice. Transplantation with mouse hepatocytes from a specific genetic model generates animals with the mutation only present in the liver. FRG KO mice transplanted with non-human primate hepatocytes (NHP) can replace the use of some experiments with primates.
For example, delivery of gene therapy can be compared between murinized, monkeynized, or humanized FRG KO mice.
To study NASH in vivo, a donor was identified that is homozygous for the G allele of rs738409 in PNPLA3. This I148M variant is significantly associated with high risk of NASH development. FRGN KO mice repopulated with human PNPLA3-148M hepatocytes and fed HFD developed key aspects of NASH.
Repopulation efficiencies were overall lower when using donors with known metabolic diseases. This was expected since many of these diseases are severe and have a detrimental impact on the health of the animal. We have been successful in transplanting either ornithine transcarbamylase (OTC) deficient hepatocytes, or maple syrup urine disease (MSUD) hepatocytes into FRG KO mice. Liver-humanized mice with a specific disease state can be of great use to study novel therapies in vivo.
Conclusion: FRG KO mice can be repopulated with hepatocytes from different species, and with hepatocytes carrying specific genetic backgrounds of interest. These liver-xenograft mice can be used either for in vivo studies, or their hepatocytes can be harvested and used for in vitro applications.

FRI299

Alpha-1-antitrypsin deficiency liver disease: patients lost in the system

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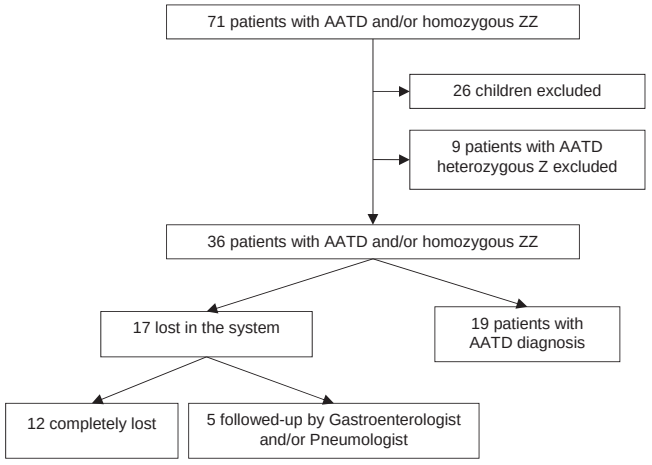
Background and Aims: Alpha-1-antitrypsin deficiency (AATD) liver disease has a very low prevalence and is considered a Rare Disease. Patients lost in the system have been described in HBV, HCV and primary biliary cholangitis. We investigate whether this problem also occurs with AATD.
Method: We included patients from 2 hospitals with homozygous genetic studies for allele Z (PiZZ) and/or AAT values ≤0.6 g/L (sensitivity and specificity >90% for PiZZ) between 2012 and 2019. Clinical reports and laboratory results from Hospital and regional databases were reviewed. Patients without specific AATD diagnosis, follow-up, or treatment were contacted and offered analysis, abdominal ultrasound, elastography and genotype. Other liver diseases were excluded. According to recent publications, elastographic cut-off points were considered: 5.45 kPa ≥ F2, 8.45 kPa ≥ F3 (AUROC 0.69 and 0.92, respectively). Liver damage in ultrasound was

considered if hyperechoic appearance of hepatic parenchyma or liver surface nodularity. The study was approved by the Ethics Committee. Variables were expressed in n (%); median (IQR 25-75).

Results: We identified 71 patients (Figure 1). Of the 36 resulting patients, 17 (47%) were classified as lost in the system (median age 64 ± 16.6 years; 59% women; median AAT value 0.5 ± 0.1 g/L; permanently normal liver biochemistry: 65%). Of these 17 patients, 5 (29%) were under follow-up by Gastroenterology/Hepatology and/or Pneumology for other reasons (fatty liver disease, chronic obstructive pulmonary disease, others) without suspected AATD. 11 patients agreed to be studied (median ± SD): platelets 243 ± 48 × 10^3/μL; ALT 26 ± 29 UI/L; HOMA-IR index 1.75 ± 2.56, BMI 21.2 ± 3.8 (0% BMI ≥ 30). Ultrasound and elastography data in 10 patients: hyperechogenicity 50%; nodularity 10%; elastography: median 5.95 ± 1.5 kPa; ≥5.45 kPa: 70%; ≥8.45 kPa: 10%.



Conclusion: Almost half of the patients with AAT deficiency are lost in the system. Of them, one half have results suggestive of liver disease, occasionally at an advanced stage.

FRI300

Neurodegenerative patterns in Wilson's disease with hepatic or neurological manifestation assessed by morphometric magnetic resonance imaging

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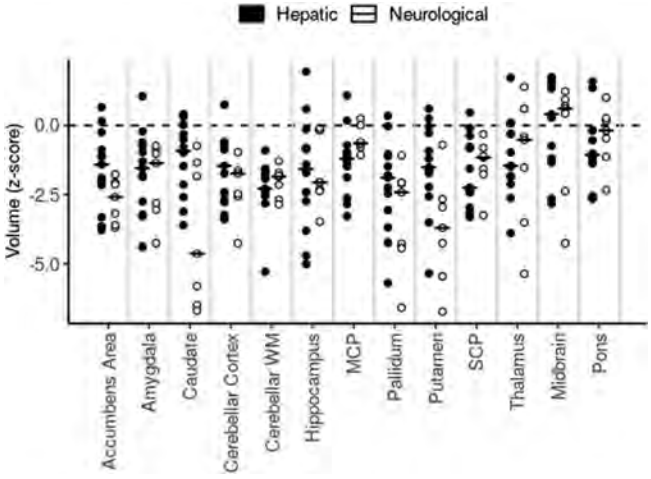
Background and Aims: Clinical presentation of Wilson disease (WD) is heterogeneous and includes hepatic and neurologic disease manifestations. Genotype-phenotype correlations failed to identify factors associated with disease expression. WD is known to cause specific qualitative neuroradiologic changes with hypo-intensities in basal ganglia known as the 'face of the giant panda' and 'eye of the tiger' signs. On neuropathological studies WD is a neurodegenerative disorder affecting the basal ganglia. The aim of the present study was to test if WD patients with predominantly hepatic or neurological phenotypic presentation show quantitative differences when magnetic resonance imaging results were analyzed by automated whole-brain segmentation procedure.

Method: Segmentation of subcortical regions from T1-weighted 3-D structural MRI data and estimation of structure volumes were carried out using the FreeSurfer tool kit (version 6.0, available at http://surfer.nmr.mgh.harvard.edu/). The volumes of the specific brain regions were expressed as Z-scores to correct for age and gender specific variations in the volume of specific segments of the brain. The study included 20 patients diagnosed with WD (13 patients with hepatic and 7 patients with neurologic WD). Liver transplant recipients were excluded. No significant differences were found when demographic genetic and baseline biochemical parameters were compared.

Results: Patients with predominantly neurological presentation showed a significant reduction in age and sex-adjusted volume of the caudate (z-score −4.64 vs −0.93, p = 0.024) and the putamen (z-score −3.72 vs −1.52, p = 0.014) when compared with the group of patients with predominantly hepatic disease manifestation. In contrast, the latter showed a significant reduction of the middle cerebellar peduncle volume (z-score −1.20 vs −0.65, p = 0.024). When all patients were compared with age and sex-matched controls, significantly reduced volumes in several brain regions could be identified, of which the most severe neurodegeneration was present in cerebellar white matter, the pallidum and cerebellar cortex. In most severely affected brain regions no difference between patients with hepatic and neurologic disease manifestations were noted.



Conclusion: This is the first study to quantitative evaluate segmentation of subcortical regions in patients with neurological and hepatic manifestation of WD. Although distinct changes were present in basal ganglia of patients with neurologic or hepatic WD, our findings indicate that WD is associated with more general pattern of neurodegeneration in patients with WD.

FRI301

Liver transplantation for acute intermittent porphyria in Europe

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Background and Aims: Since the first report on liver transplantation (LT) for acute intermittent porphyria (AIP) in 2004, LT has become an established treatment option for patients with severe recurrent disease and poor quality of life. The outcomes after LT have been reported in an early case series and a few case reports. We aim to describe pre-transplant morbidity, transplant complications, outcomes and survival for all adult LTs for AIP in Europe.
Method: Cases were identified by searching the European Liver Transplant Registry (ELTR), previous publications and by personal communications. A questionnaire was sent to identified transplant centres or managing physicians. Data compilation focuses on 1) demographics & clinical porphyria characteristics, 2) transplant related factors and 3) post-transplant outcomes including survival, renal function and neurological impairment.
Results: The case search identified 40 AIP patients. We have data on 36 to date, 32 females and 4 males, from 12 countries who were transplanted in Europe 2002–2019. Median age at LT was 37 years (18–58) and median follow up time 5.2 years (0.2–14.5). Hepatic artery thrombosis occurred in 4 cases (12%). Two patients were retransplanted and 9 died during the follow-up period. The 1-year and 5-year overall survival rates were 91% and 81%. Renal impairment was identified as a risk factor for poor outcome. Neurological impairment improved after LT: e.g. mobility was impaired in 39% at LT compared to 14% at follow-up. Renal function was impaired in 55% at LT and improved in a minority of patients after LT but no improvement in the mean GFR was noticed. No patients had AIP symptoms after LT.
Conclusion: Liver transplantation is an important treatment option for patients with severe recurrent AIP. Survival is equal to other transplantation indications and all patients were cured from the AIP. Renal impairment is a risk factor for poor outcome and most patients show no improvement in GFR after LT. Neurological function improves after transplantation.

FRI302

Magnetic resonance iron quantification facilitates venesection decision making in iron overload

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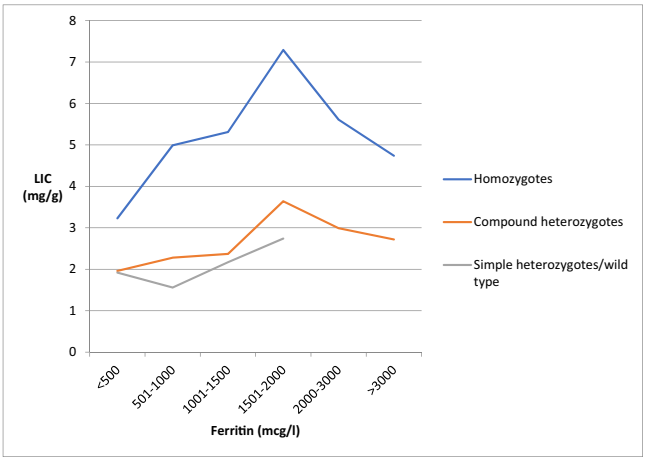
Background and Aims: Venesection is the standard treatment for hereditary haemochromatosis (HH) preventing morbidity and mortality however in some groups the clinical benefit of therapeutic venesection may be negligible. Furthermore the degree of ferritin elevation may overestimate the true extent of iron overload. In order to help inform practice we analysed magnetic resonance (MR) iron quantification data in a cohort investigated for HH.
Method: A cross-sectional study of 87 patients, without known liver or haematological disease, was undertaken. All subjects underwent HFE genotyping and MR imaging with hepatic iron quantification. Additional risk factors for liver disease were noted: alcohol excess, fatty liver, obesity (BMI > 30). Serum ferritin and transferrin saturation values were time-matched with MR liver iron concentration (LIC).
Results: The cohort comprised 39 C282Y homozygotes, 23 compound heterozygotes (C282Y/H63D) and 25 either simple C282Y heterozygote or wild-type. Of 39 C282Y homozygotes (17 females, 22 males, mean age 59), 15/39 (38%) had liver risk factors. Serum ferritin ranged 184–3000 mcg/l (mean 1062 mcg/l), transferrin saturation 43–100% (mean 81%), and LIC 1.27–9.97 mg/g (mean 5.02 mg/g, 1/39 in normal range). There was no difference between those with liver risk factors and those without regarding either serum ferritin (1131 vs 1021 mcg/l) or LIC (4.68 vs 5.23 mg/g).
Of 23 compound heterozygotes (5 females, 18 males, mean age 55), 21/23 (91%) had liver risk factors. Serum ferritin ranged 418–3016 mcg/l (mean 1033 mcg/l), transferrin saturation 29%–100% (mean 51%) and LIC 1.36–4.58 mg/g (mean 2.43 mg/g). 6/23 (26%) had LIC in the normal range with mean serum ferritin 659 mcg/l. A serum ferritin of 1000 mcg/l had 92% sensitivity and 50% specificity for the detection of significant iron overload (>2.5 mg/g).
In the remaining group (3 females, 22 males, average age 65), 15/25 (60%) had liver disease risk factors. Serum ferritin ranged 351–1957 mcg/l (mean 1113 mcg/l), transferrin saturation 21%–96% (mean 46%) and LIC 1.41–4.23 mg/g (mean 2.11 mg/g). 10/25 (40%) had LIC in the normal range with mean serum ferritin 1031 mcg/l. Those with liver risk factors had higher serum ferritin (1254 vs 901 mcg/l, $p < 0.05$) with comparable LIC (2.19 vs 1.97 mg/g).
LIC was significantly higher in homozygotes compared with the other groups for any given ferritin concentration (see figure).



Conclusion: Compared with C282Y homozygotes, liver risk factors are more common in other HFE genotypes, especially compound heterozygotes, and contribute to serum ferritin values. In non-homozygotes around 1/3 have LIC in the normal range despite significant hyperferritinaemia. Compound heterozygotes with serum ferritin >1000 mcg/l are more likely to benefit from venesection.

FRI303

Major depressive disorder in patients with Wilson's disease: relationship with liver disease, neurological disease and quality of life

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Background and Aims: Mental health problems are underappreciated in Wilson disease (WD) (Schaefer et al. 2016. *Clin Res Hepatol Gastroenterol*, 40(3):349–356). We aimed to determine: i) the prevalence and clinical features of major depressive disorder (MDD) in adults with WD ii) whether MDD is related to liver and neurological disease and quality of life (QOL).
Method: A multi-site WD registry was initiated in December 2017. At enrollment adults (n = 55) were evaluated using questionnaires and

administered exams assessing cognition, mood, psychosis, substance use, anxiety, perceived stress, personality change and QOL. MDD was determined using the MINI-7. Patients underwent hepatology and neurological assessments (UWDRS). We reviewed depression at first presentation and diagnosis. Statistical analyses included Wilcoxon Rank Sum test, Chi-squared test or Fisher's exact test.

Results: Depression was self-reported in 25% at first presentation of WD (29% at diagnosis). At enrollment, 40% had a lifetime history of MDD, 9 with MDD took antidepressants; 10 reported historic use. Cirrhosis was present in 23% based on imaging, APRI and Fib4. We found no significant difference in MDD (36% vs 42% p = 0.74) or depression symptomology based on PHQ-9 score (median 2 vs 4, p = 0.08) in cirrhotics vs non-cirrhotics. Liver disease severity did not differ in cirrhotics with MDD and those without (median Child-Pugh 5 (5–9) vs 5 (5–9), p = 0.92; MELD-Na 7 (6–12) vs 8 (7–13), p = 0.18). Two patients (1 with MDD) took medication for hepatic encephalopathy. No significant difference in neurological UWDRS total scores was found in those with MDD vs without (median 8.5 (0–73) vs 5 (0–45), p = 0.22). A UWDRS total score >0 was not found to be associated with MDD (77.3% vs 81.8%, p = 0.74).

Patients with MDD had worse mental health QOL (median 42.3 vs 54.6 p < 0.01), more suicidal ideation (36% vs 3% p = 0.002), higher anxiety (median 3.5 vs 3 p = 0.049), higher perceived stress (median 19 vs 9 p < 0.001), and more neuroticism (median 7 vs 5, p = 0.005). We found no significant difference in physical health QOL in MDD (median 54 vs 56.7 p = 0.34).

Conclusion: MDD is highly prevalent in WD and associated with worse mental health QOL. The risk appears higher than other chronic liver diseases (Lee et al. 2013. *Psychosomatics*, 4:52–9). We did not find a statistically significant association between the severity of liver, neurological disease and MDD. Screening for depression should be considered in patients with WD.

FRI304

Mortality in patients with Wilson's disease in England: a national register-based study

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Background and Aims: Wilson Disease (WD) is a rare genetic disorder of copper metabolism. Without appropriate treatment it can progress to liver failure and death. The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS), with support from the British Association for the Study of the Liver WD Special Interest Group, has established registration of WD in England. We aim to provide a descriptive study of mortality, including multiple cause of death and transplant status, of those with WD.

Method: Confirmed cases of WD were reported by 20 hospital trusts and registered with NCARDRS enabled by their legal permissions (CAG 10-02(d)/2015) to collect patient data without consent. Vital status of all cases were determined and linkage with Office of National Statistics (ONS) mortality data was undertaken to obtain death certificate data. Cases of *E83.0 Disorders of copper metabolism*, between 2008 and 2018, were extracted from ONS mortality data. Cause of death free text was manually searched to identify deaths that mentioned WD. All deaths were linked to Hospital Episode Statistics (HES) inpatient data to determine transplant status.

Results: Death records were identified for 52 patients, with a mean age of 45.5 years (range 17–82), 65% were male. Complications related to cirrhosis or liver failure were assigned as the underlying cause of death (UCOD) in 44%. Hepatocellular carcinoma (HCC) was the UCOD in 5.8%. Of the 21% of patients who were recorded as having a liver transplant, transplant complications or graft failure were recorded as a cause of death in 8%. Sepsis was mentioned on the death certificate in 42% and recorded as the UCOD in 21%.

Table: Underlying cause of death in WD.

UCOD	Assigned on death certificate (%)	Assigned by ONS (%)
WD	40	44
Transplant	8	2
Infection[a]	29	21
HCC	4	5.8
Bleeding	6	2
Liver disease (other)[b]	0	2
Chronic illness	0	5.8
Accident	0	5.8
Cancer	2	5.8
Other	11	5.8

[a]Includes cirrhosis, decompensated disease, liver failure.
[b]Includes spontaneous bacterial peritonitis, biliary, viral and fungal.

Conclusion: The contribution of WD to mortality in England will be underestimated unless multiple cause of death analysis is undertaken. The number of deaths resulting from complications related to cirrhosis or liver failure suggests that there might be missed opportunity for liver grafting. HCC was the cause of death in 5.8% of cases suggesting the prevalence of HCC in WD may be higher than previously thought. This project demonstrates the utility of the NCARDRS for WD in England.

FRI305

Survival in HFE hemochromatosis: influence of polymorphisms in HSD17B13, GNPAT, and PCSK7

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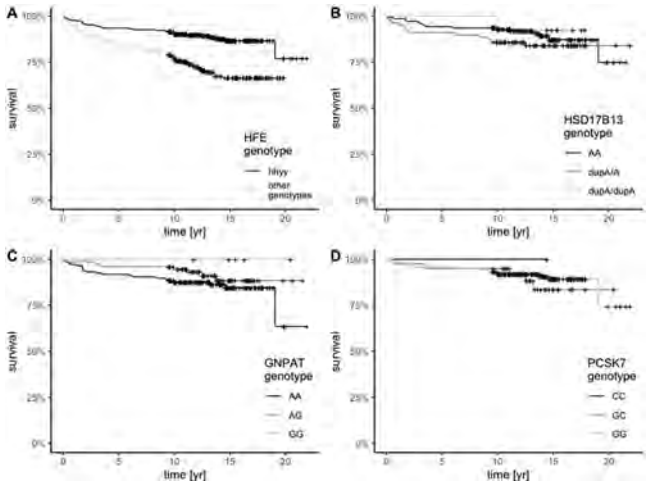
Background and Aims: Hereditary hemochromatosis, defined as homozygosity for the p.C282Y polymorphism in the HFE gene, is a condition of iron overload with variable penetrance. The polymorphism affects endogenous iron homeostasis by impairing transferrin receptor mediated hepcidin response. Various genetic modifiers have been postulated to modify the disease phenotype in persons with this genetic constellation, with conflicting results when serum iron parameters or the degree of liver disease were used as statistical endpoints. In a cohort of 438 patients presenting for workup of hyperferritinemia, survival was assessed in relation to the presence of polymorphisms in HSD17B13, GNPAT, and PCSK7, as well in relation to the HFE genotype.

Method: In a cohort of 438 patients having presented at LKH Innsbruck for genetic workup of hyperferritinemia, HFE genotyping was routinely performed. Serum iron parameters were recorded simultaneously, together with a staging of liver disease. Additionally, alcohol intake was recorded. Survival data were available for the entire cohort as of Oct 1, 2019. For this study, pseudonymized samples were additionally genotyped for polymorphisms rs72613567 in the HSD17B13 gene, rs11558492 in the GNPAT gene, and rs236918 in the PCSK7 gene. Principal component analysis (PCA), Kaplan-Meier survival estimates and Cox proportional hazard models were calculated in R in a manner of right-censored data. Stratification for iron overload was performed using EASL criteria, i.e., gender specific cutoffs for ferritin (FTN) of 300 µg/L and 200 µg/L as well as 50% and 45% in transferrin saturation, in male and female persons, respectively. Minor allele frequencies were compared to gnomAD Genomes (subset, european population).

Results: Out of 230 patients homozygous for the HFE p.C282Y polymorphism, 182 met EASL criteria of iron overload. Criteria for Hardy-Weinberg equilibria were met for all three polymorphisms studied, minor allele frequencies did not significantly differ in comparison to the general population. Serum iron parameters were not significantly different in dependence of polymorphisms. Survival was not different in any of the three polymorphisms studied. Results were similar in the subset with elevated serum iron parameters.



Conclusion: Iron overload syndrome caused by type I hereditary hemochromatosis has a better prognosis as compared to non-HFE iron overload. HSD17B13, GNPAT and PCSK7 showed no relevant effects on outcome.

FRI306

Analysis of survival and influence of genetic modifiers in HFE- and non-HFE-associated iron overload

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Background and Aims: The most common form of hereditary iron overload is linked to homozygosity for the p.C282Y polymorphism in the HFE gene, resulting in an impaired hepcidin response. A large proportion of patients with clinically relevant iron overload, however, does not carry this genetic constellation, the iron overload then being classified as non-HFE hemochromatosis. Iron overload is one of many potential risk factors of chronic liver disease and is in itself influenced by both other genetic modifiers, concurrent diseases, and external factors. Survival as a potential end-point of iron overload syndromes is rarely reported.
Method: In a cohort of 438 patients having presented at LKH Innsbruck for genetic workup of hyperferritinemia, HFE genotyping was routinely performed. Serum iron parameters were recorded, together with a staging of liver disease, and alcohol intake. Survival data were available for the entire cohort as of Oct 1, 2019. For this study, samples were additionally genotyped for polymorphisms rs72613567 in HSD17B13, rs11558492 in GNPAT, and rs236918 in the PCSK7 genes. Principal component analysis (PCA), Kaplan-Meier survival estimates and Cox proportional hazard models were calculated in R in a manner of right-censored data. Stratification for iron overload was performed using EASL criteria, i.e., gender specific cutoffs for ferritin (FTN) of 300 µg/L and 200 µg/L as well as 50% and 45% in transferrin saturation, in male and female persons, respectively.
Results: Survival is markedly reduced in non-HFE hemochromatosis patients as compared to patients homozygous for HFE p.C282Y (hazard ratio, 2.75, $p < 0.001$). This difference is strongest in the subset of patients with elevated serum iron parameters (HR, 6.57, $p = 0.001$), further illustrated by PCA analysis. Alcohol intake (HR, 2.19, $p = 0.03$) and advanced liver disease (HR, 3.21, $p < 0.001$) additionally proved to be associated with mortality in non-HFE patients. Effects of putative genetic modifiers of iron homeostasis were stronger in the non-HFE subset.
Conclusion: Iron overload syndrome caused by type I hereditary hemochromatosis (homozygosity for HFE p.C282Y) has a better prognosis as compared to non-HFE hemochromatosis. This is most likely a consequence of the fact that significant iron overload in the absence of the strongest genetic modifier is most likely caused by multiple, less obvious concurrent risk factors that generally are more challenging to control.

FRI307

Validation of the new proposed histological criteria for the diagnosis of porto-sinusoidal vascular disease in a single tertiary center

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Background and Aims: Recently, a new definition of porto-sinusoidal vascular disease (PSVD) has been proposed. An adequate liver biopsy is still mandatory for PSVD diagnosis. However, many histological features are also found in chronic portal vein thrombosis (PVT).
The study aims to validate the new proposed histologic criteria in a cohort of PSVD patients and to test these criteria in patients with PVT.
Method: Patients diagnosed with PSVD between 2016 and 2019 at our center were included. All liver biopsies were reviewed by an expert pathologist and were classified according to the new criteria: specific signs (obliterative portal venopathy-OPV, nodular regenerative hyperplasia-NRH, and incomplete septal fibrosis ISF), non-specific signs (portal tract abnormalities, architectural disturbances, non-zonal sinusoidal dilatation, and mild perisinusoidal fibrosis). Patients without clinical signs of portal hypertension (PHT) but who had a positive liver biopsy were also included. A small cohort of patients diagnosed with PVT that had liver biopsies performed was also included.
Results: Thirty-three patients (28 with PSVD and 5 PVT) were included. Mean age was 40.52 years [19–72], 48.5% females, MELD score of 9 [6–17]. Twenty-six (93%) patients with PSVD and all patients with PVT had PHT signs at diagnosis. The two patients without PHT signs at diagnosis performed liver biopsies for the alteration of liver enzymes. Twenty-three (82%) patients with PSVD and all patients with PVT had adequate biopsies: median length of 28.48 mm [7–49] and 36.8 mm [23–54], respectively, and the total number of portal tracts of 19.41 [8–40] and 23.8 [15–35], respectively. In the PSVD group, 22 (78.6%) patients had specific criteria (19-OPV, 10-NRH, and 1-ISF), and 24 (88.9%) patients had non-specific criteria (19-portal tract abnormalities, 1-architectural changes, 19-sinusoidal dilatation, and 14-mild perisinusoidal fibrosis). In the 2 PSVD patients without signs of PHT, the liver biopsies showed major criteria (2-OVP) as well as minor criteria. In the PVT group, all patients had major as well as minor criteria on liver biopsy.
Conclusion: The new proposed histologic criteria for the diagnosis of PSVD is feasible in patients with or without PHT. Although the present cohort was very small, in patients with PVT, the histological signs were very similar to that of PSVD. More studies should focus on the histological differentiation between the two entities.

FRI308

Non-invasive diagnostic tools in porto sinusoidal vascular liver disease. A pilot study

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Background and Aims: Porto sinusoidal vascular liver disease (PSVD) represents a cause of presinusoidal portal hypertension which can often lead to formation of oesophageal or gastric varices and portal hypertension related bleeding. In cirrhotic patients, liver stiffness measurement by transient elastography (LSM) < 20 kPa and platelets (PLT) count >150.000 are able to rule-out high risk oesophageal varices. However, in patients PSVD there is no non – invasive test that can predict the presence of varices. We aimed to investigate whether LSM, spleen stiffness measurement (SSM) and PLT count have a role in prediction of varices in patients with PSVD.
Method: Patients diagnosed with PSVD who were admitted at the RIGH 'Prof. dr. Octavian Fodor' and who had performed endoscopies prior to or at enrolment were included in the study. All patients had routine laboratory work out and performed liver and spleen measurements by transient elastography with a Fibroscan 502 Touch® (M or XL probe). The median of 10 measurements with an IQR < 0.3 was considered adequate. A control group of cirrhotic of various etiologies compensated patients was also included in the study.
Results: Nineteen patients with biopsy proven PSVD were included in the study. Mean age was 34.79 years [range 19–72] and included 57.9% of male patients. All patients were Child Pugh A and had a mean MELD score of 9.31 [range 6–17], mean PLT level was 120.000 [range 12.000–325.000]. Fifteen patients of the patients had varices, either esophageal (n = 11), gastric (n = 2) or both (n = 1). Mean LSM was 9.3 kPa [range 3–39.7] and mean SSM was 46.9 kPa [11.8–75]. The ratio between the difference of SSM and LSM and PLT count ((SSM-LSM)/PLT) was the best test to predict the presence of varices with an AUROC of 0.83 CI 95% (0.64–1), p = 0.04. If the (SSM – LSM)/PLT ratio was <0.06, the test had a sensitivity of 100%, specificity of 25%, a PPV of 83% and a NPV of 100% with a +L = 1.33 and a – LR = 0 in prediction of varices. The test had a diagnostic accuracy of 84.2% (16 / 19). If the (SSM – LSM)/PLT ration was > = 0.29, the test had a sensitivity of 66%, specificity of 100%, a PPV of 100% and a NPV of 44% with a + L = infinite and a – LR = 0.33 in prediction of varices. When this ratio was tested in the cirrhotic population, the AUROC was 0.32 CI 95% (0.13–0.53), p = 0.13.
Conclusion: The ratio of (SSM-LSM)/PLT has a high accuracy for predicting esophageal or gastric varices in patients with porto sinusoidal vascular liver disease, but not for patients with compensated cirrhosis. At a cut – off of 0.06, the test has a very large effect on ruling-out and at a cut-off of 0.29 the test has a very large effect on ruling-in the presence of varices in this disorder. In these patients, according to these cut-offs, endoscopies should be performed if the ratio is between 0.06 and 0.29. Due to small sample size and high prevalence of varices, these results need confirmation in a larger cohort.

FRI309

Simplification of Wilson's disease maintenance therapy with a single daily dose: safety and efficacy in difficult to treat patients

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Background and Aims: Wilson's disease (WD) is a rare genetic disease responsible for deleterious accumulation of copper in different organs, mainly in the liver and brain. There are effective medications for the treatment of this affection but according to recommendations the drugs have to be taken 2 or 3 times a day all-lifelong, which may limit adherence to treatment and therefore therapeutic efficacy. Single daily dose (SDD) is a good way to improve adherence by simplification of therapy. In the French National Reference Center for WD of Lyon, some patients are currently on single daily dose of D-Penicillamine, Trientine of Zinc, either by personal choice or by physician choice. The goal of our study was to report the efficacy of single daily dose of treatment in WD patients.
Method: We reviewed the chart of all WD patients followed in our center. Patients with an history of SDD of WD treatment were included in this retrospective study. The treatment failure was defined as a composite criteria with the occurrence of at least one of the following criteria : death, transplantation, increase of transaminases >2 × ULN, hepatic decompensation, neurological aggravation, severe side effect related to treatment and/or discontinuation of treatment for more than a week. The rate and the time to first failure after SDD were reported.
Results: We identified 14 patients with a past history of non-adherence who received a SDD of WD therapy: 6 males and 8 females, with a mean age at diagnosis of 12,9 yrs. There were 6 hepatic, 6 extrahepatic and 2 presymptomatic forms. The switch to SDD was performed after a median delay of 151 months after diagnosis. Eight, five and one patients were respectively on SDD of Trolovol, trientine and Wilzin. Two patients were considered as non-stabilized before the switch: one patient had cytolysis >2 × ULN and one patient had neurological aggravation related to treatment discontinuation. After one year of SDD, only one patient (7%) met criteria for treatment failure with the occurrence of cytolysis >2 × ULN though the liver function tests (LFT) were initially normal. The two non-stabilized patients had clinical improvement (normalization of LFT, amelioration of UWDRS neurological score). After a median delay of 41 months on SDD, 3 patients (21%) had treatment failure (2 cytolysis and 1 treatment discontinuation). There were no death, no liver transplantation, no hepatic decompensation, no neurological deterioration and no severe side effects related to treatment during the follow-up. Moreover ALT, AST and exchangeable serum copper were not statistically different after one year of SDD and at last news compared to baseline.
Conclusion: Simplification of maintenance therapy with a single daily dose is an option to consider in difficult-to-treat Wilsonian patients. In this pilot study, SDD was effective in around 80% of patients without any concern regarding safety.

FRI310

A phase 1/2 open label extension study of givosiran, an investigational RNAi therapeutic, in patients with acute intermittent porphyria

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Background and Aims: Acute intermittent porphyria (AIP) is a rare genetic disease caused by an enzyme deficiency involved in heme biosynthesis. Induction of 5-aminolaevulinic acid synthase 1 (ALAS1) leads to accumulation of toxic heme intermediates, 5-aminolevulinic acid (ALA) and porphobilinogen (PBG), resulting in potentially life-threatening, neurovisceral attacks and chronic symptoms. Givosiran, an investigational RNAi therapeutic, specifically targets ALAS1 to reduce ALA and PBG levels.
Method: A Phase 1 study evaluated the safety, tolerability, and pharmacokinetics/pharmacodynamics of givosiran (NCT02452372). Part C of the study was conducted in AIP patients experiencing recurrent attacks and included clinical activity as an exploratory endpoint. Patients completing Part C were eligible to enroll in the Phase 1/2 open-label extension (OLE) study (NCT0294983).
Results: As of April 19, 2019 (median time on study 24.7 months), givosiran administered at 2.5 mg/kg monthly robustly lowered ALA and PBG from baseline by >85% at 18 months in a sustained manner (median follow-up 19.8 months). Patients on givosiran had substantial mean reductions of >90% in annualized attack rate (AAR) and annualized hemin use, relative to Phase 1 Run-in. Serious adverse events (10) were reported in six patients, with one case of anaphylaxis assessed as definitely related to study drug. Adverse events occurring in more than three patients included abdominal pain, fatigue, injection site erythema, nausea, nasopharyngitis, headache, myalgia, diarrhea, injection site pruritus, and international normalized ratio increased. Seven patients had injection site reactions, all mild to moderate. No clinically significant laboratory changes were observed, including liver function tests.
Conclusion: In an ongoing Phase 1/2 OLE study, givosiran has shown an acceptable safety profile and has been associated with marked and sustained reductions in both AAR and annualized hemin use. Updated data from this study will be presented.

FRI311

Good clinical outcomes after direct intrahepatic portocaval stent (DIPS) insertion for Budd-Chiari syndrome

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Background and Aims: Budd Chiari syndrome (BCS) is rare but potentially life-threatening condition. Recanalization using TIPSS or hepatic venous stenting is key to relieving hepatic congestion. These procedures are impossible in complete HV occlusion. Direct intrahepatic portocaval shunt (DIPS) is a new procedure where a stent is placed directly from the inferior vena cava, often through the caudate lobe to the portal vein bypassing the thrombosed HVs. We report our experience in using DIPS for recanalization in BCS.
Method: Single centre retrospective analysis from May 2015 to January 2019 comparing outcomes following a DIPS insertion compared to our centres previously published data*.
Results: 14 patients were referred for a DIPS procedure. M:F ratio 8:6; age 40.5 ± 13.2; follow up 23.1 ± 15.0 months. HV-BCS type in all. Aetiology: myeloproliferative neoplasm (MPN) in 7, all JAK2+ve with mutation load 17.3 ± 10.2%; PNH, 1; idiopathic, 6 (all –ve following next generation sequencing). Pre-DIPS: MELD 13.1 ± 3.2, UKELD 49.1 ± 13.35, BCS-TIPS PI score 4.45 ± 1.1**. Post DIPS portal pressure gradient was 6.9 ± 2.2 mmHg. Clinical indication: variceal bleeding and ascites (n = 1) or ascites (n = 13). Multidisciplinary consensus to undertake a DIPS insertion as a first line procedure was reached in 13 patients, in 1 patient a TIPSS insertion was initially attempted, when this failed a rescue DIPS was performed. One DIPS insertion (7%) was not successful, this patient is now on the waiting list for transplantation, all of the others patients were successful stent placement and none required escalation to transplantation. Ascites resolution was seen in 7 out of 11 patients at follow up (64%). 2 patients developed hepatic encephalopathy post DIPS (14%). Primary patency rates at 6 months, 1 year, and 2 years were 83%, 83%, 58% respectively. Secondary patency was 100%. Transplant free survival 100% to date. The outcomes are comparable to a previously reported series from the same institution, with similar BCS-TIPS PI but slightly lower MELD.*
Conclusion: Our data demonstrates that with technical excellence, multidisciplinary management, and careful patient selection, DIPS results in very good clinical outcomes in patients unsuitable for standard TIPSS. The outcomes are comparable to standard TIPSS from our historic data.* We strongly recommend early referral of all patients with BCS to multidisciplinary teams in centres that offer advanced interventional radiology and liver transplantation.

* Tripathi D, et al. Long-term outcomes following percutaneous hepatic vein recanalization for BCS. Liver Int. 2017 Jan;37(1):111–120.
** (age(years) × 0.08) + (bilirubin (mg/dL) × 0.16) + (INR × 0.63).

FRI312

Clinical features and natural history of 1154 Alagille syndrome patients: results from the international multicenter GALA study group

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Background and Aims: Alagille Syndrome (ALGS) is a rare multi-system disorder and one of the most common inherited causes of neonatal cholestasis. Prior ALGS studies largely come from tertiary liver centers and therefore select for the most severely affected cholestatic patients. As a result, the full spectrum of ALGS liver involvement remains unclear. Also, a comprehensive assessment of extrahepatic manifestations in a large cohort is missing. The Global ALagille Alliance (GALA) Study Group was established to overcome these limitations.

Method: Multicenter retrospective analysis of children with a clinically and/or genetically confirmed ALGS diagnosis, born between Jan-1997 and Aug-2019. Histopathological features in liver biopsies were compared with chi-square. Cox proportional hazards models were constructed to determine transplant-free survival (TFS) in ALGS patients who underwent a Kasai or biliary diversion (BD). TFS and overall survival were estimated using the Kaplan-Meier method.

Results: 1154 ALGS (58% male) patients from 25 countries were included (median follow-up 5.6 years, IQR 2.3–11.3). Of the 75% genetically confirmed patients, 93% have a mutation in *JAG1* and 4% in *NOTCH2* (69% *de novo*). Any cardiac anomaly was the most common extrahepatic manifestation (89%), followed by characteristic facies (88%), posterior embryotoxon (49%), butterfly vertebrae (44%), and renal anomalies (35%). MRI and CT reports revealed cerebral and intra-abdominal vascular anomalies in 34% and 31% of patients, respectively. Review of 497 baseline liver biopsy reports (Table) revealed an increasing frequency of bile duct paucity with age ($p = 0.01$) and features of biliary obstruction in 20% of biopsies <6-months. 10-and-18-year TFS rates in 911 ALGS patients presenting with neonatal cholestasis were 57% and 41%, respectively. ALGS patients who underwent a Kasai (n = 74, HR 3.3, 95% CI 2.4–4.5; $p < 0.001$) or BD (n = 46, HR 2.0, 95% CI 1.4–3.7; $p = 0.004$) had significantly lower rates of TFS. Overall 10-and 18-year survival rates were 90.9% and 88.6%, respectively.

Table: Histopathological features in 497 baseline liver biopsies.

	Biopsy <6 months	Biopsy ≥6 and <24 months	Biopsy ≥24 months	P-value
n	307	84	106	
Histopathologic Findings, % (*n*)				
Bile duct paucity	61 (188)	63 (53)	77 (82)	0.01
Giant cell transformation	40 (124)	12 (10)	4 (4)	<0.001
Bile duct proliferation	20 (62)	18 (15)	7 (7)	0.005
Duct/ductular bile plugs	7 (20)	5 (4)	2 (2)	0.20

Conclusion: We describe the largest global cohort of ALGS to date. Almost 60% of ALGS children with neonatal cholestasis will undergo liver transplantation by the age of 18 years. ALGS patients who underwent a Kasai procedure had significantly lower rates of TFS – it remains to be seen if this is due to a more severe hepatic phenotype in these patients, or if Kasai adversely affects hepatic natural history. This dataset provides a robust foundation for future clinical studies in ALGS.

FRI314

Wilson's disease: epidemiologic and therapeutic insights from German hospital and ambulatory invoicing data

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Background and Aims: Wilson's disease (WD) is an autosomal recessive inherited condition in which copper excretion via bile is diminished due to gene mutations in the ATP7B gene. Consequence is a toxic accumulation of copper in predominantly the liver and the brain leading to a variety of hepatic and neurologic symptoms. WD prevalence in Germany is often estimated around 1:30,000. Little is known about the medical treatment and hospitalization rate of patients in Germany. Here we used health insurance billing data to estimate the current number and care of WD patients.
Method: Inpatient care data from Federal Statistical Office 2005–2017 and ambulatory billing data from the federal physicians' organization and quality reports for 2009–2017 of all German hospitals were evaluated for WD encodings and treatment schemes. Analysis with IBM SPSS-25.
Results: In 2017 there were 1,368 patients in German statutory sick funds diagnosed with the fitting ICD E83.0 for WD and received a WD specific therapy. Thereof 828 (60.5%) D-penicillamine, 217 (15.9%) trientine, 174 (12.7%) zinc-acetate and 149 (10.9%) other zinc-salts. 46.4% of treated patients are women, they make 45.7% of all chelator and 48.1% of all zinc therapies. The prevalence related to diagnosed and treated patients was around 1:60.000. The relation of chelators to zinc therapy was very stable from 2009 to 2017. Patients younger than 24 years were treated relatively more frequently with chelators than adults. The number of diagnosed patients under 15 years hardly changed from 159 (2009) to 161 (2017). Regional distribution of WD diagnoses was rather similar throughout Germany.
186 patients were hospitalized with WD as main diagnosis in 2017. Thereof 45.1% female, who stay shorter in hospital (6.2 days) than men (8.5 days). 45.2% of cases are treated in neurologic departments, 29.0% in gastroenterological and 19.9 in pediatric departments; 3.2% in transplant units (2.7% other). Stays in neurologic departments take longer, such that more than half of hospital days are spent there. Regional distribution of hospitalization differs widely and is not related to ambulatory cases, from 4.9 per million in Rhineland to 11.8 per million in Pomerania. Mean age at hospitalization with main diagnosis WD is 30.1 years (m 29.9 y, f 30.3). Around 48% of patients are treated in university hospitals.
Conclusion: The German billing data allows for a quite exact estimation of diagnosed and treated patients with WD. From 2009 to 2017 treatment patterns did hardly change. Younger patients are treated more frequently with chelators than adults. Hospitalizations are partly driven by regional habits. Men stay more frequently and longer in hospital. A national registry would support further insights.

FRI315

The role of liver stiffness by ARFI elastography in the diagnosis of porto-sinusoidal vascular disease: comparison with patients with chronic portal vein thrombosis

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Background and Aims: PSVD (porto-sinusoidal vascular liver disease) and PVT (portal vein thrombosis) are distinct vascular liver diseases characterized respectively by an intrahepatic and a pre-hepatic obstacle to the flow in the liver portal system. PVT may also occur as a complication of the natural history of PSVD, especially if a pro-thrombotic condition coexists.
The presence of PSVD should be suspected in patients with PVT and its active search be included in their diagnostic work-out. However, sometimes the diagnosis of pre-existing PSVD is very hard. Liver stiffness (LS) may help as it has been shown to be higher in PSVD than in "pure" PVT but this comparison is until now restricted to very limited series of patients. The aim of the study is to compare LS between the two groups of patients and to find a cut-off value of LS to discriminate the two diseases.
Method: Forty-six patients affected by histologically proven PSVD and fifty-five patients affected by chronic PVT were enrolled. Laboratory, endoscopic and ultrasonographic data were collected. LS was measured by ARFI (acoustic radiation force impulse).

Table: Comparison between patients with PSVD and chronic PVT.

	PSVD (n = 46)	Chronic PVT (n = 55)	P value
Age (mean ± SD)	49 ± 15	52 ± 14	NS
Sex (M/F)	31/15	27/28	NS
Bilirubin (mg/dl)	1.1 ± 0.6	1.2 ± 0.6	NS
Albumin (g/dl)	4.2 ± 0.6	4.6 ± 0.4	NS
Platelet ($\times 10^3/\mu l$)	133 ± 129	278 ± 178	0.0001
Esophageal Varices (absent/small/large)	16/14/16	19/19/17	NS
Previous Variceal bleeding (No/Yes)	29/17	35/20	NS
Ascites (No/Yes)	42/4	39/16	0.01
Spleen Diameter (cm)	18 ± 4	17 ± 5	NS
ARFI (KPa)	**7.4 ± 7**	**4.6 ± 2**	**0.005**

Results: The results of the comparison between the two groups of patients are summarized in the table. Liver stiffness was significantly higher in patients affected by PSVD than in patients with chronic PVT. Based on the results of ROC analysis, the best cut-off of LS to distinguish the two groups of patients was 7 KPa, with a sensitivity of 90% and specificity of 53%.
Conclusion: Our study showed that liver stiffness measured by ARFI is higher in patients with PSVD than in patients with chronic PVT. A cut-off value of 7 KPa has been identify but needs to be confirmed by more studies with a higher number of patients.
Even if still to strengthen, our findings may have clinical consequences, especially in the decision of performing a liver biopsy in patients with PVT and a higher liver stiffness and suspending the anticoagulation in patients with PVT and no detectable pro-thrombotic factors.

FRI316

Elevated serum bile acid and alanine aminotransferase concentrations in intrahepatic cholestasis of pregnancy are associated with increased fetal NT-proBNP which is ameliorated by ursodeoxycholic acid treatment

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Background and Aims: Intrahepatic cholestasis of pregnancy (ICP), diagnosed by elevated maternal total serum bile acid (TSBA) concentrations and pruritus, is associated with fetal cardiac dysfunction that is thought to cause the increased rate of stillbirth observed in severe forms of the disease. We aimed to investigate the relationship between severity of deranged markers of liver function shown in ICP and fetal NT-proBNP, a marker of heart failure, at birth and assess the effect of ursodeoxycholic acid (UDCA) treatment.
Method: Serum samples were collected between 1 and 21 days before birth from 17 women with uncomplicated pregnancies (defined as controls) and 68 women with ICP (35 of whom were untreated and 33 UDCA-treated) from St. Thomas' and Queen Charlotte's and Chelsea Hospitals (London, UK). TSBA, alanine aminotransferase (ALT) and bilirubin concentrations were tested in-

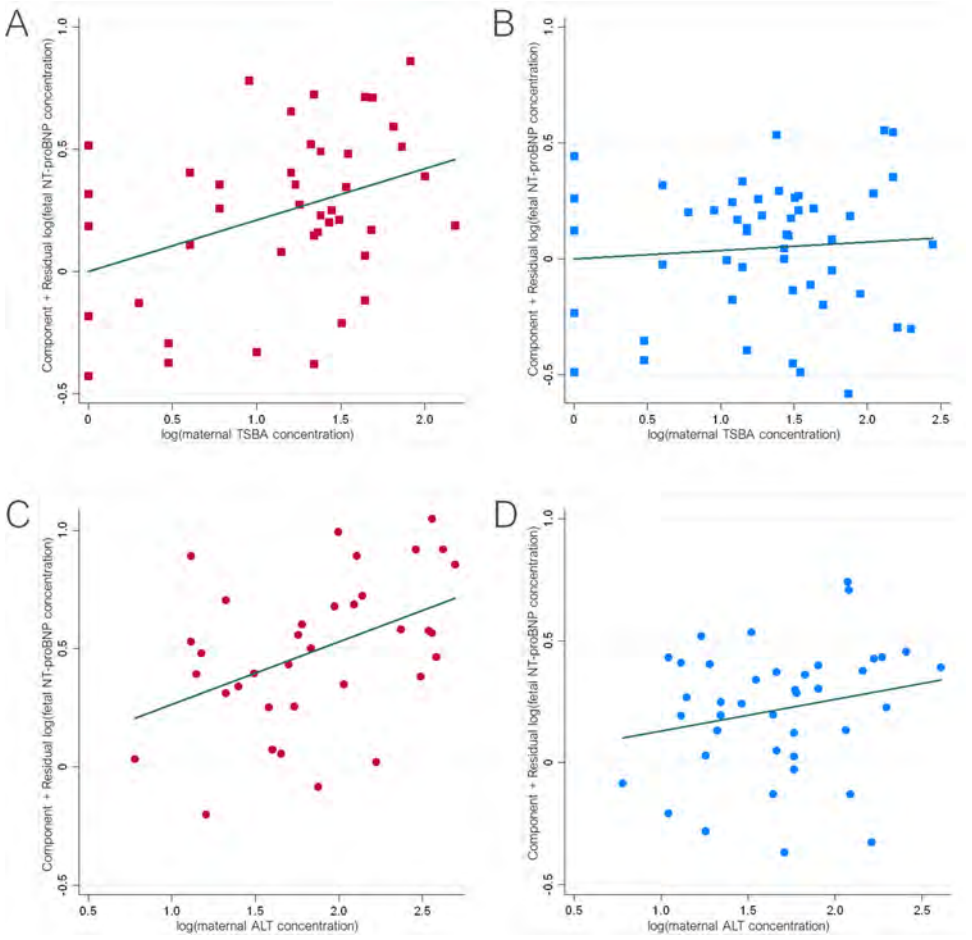

Figure 1: (abstract: FRI316)

house by pathology laboratories. Umbilical cord serum samples were collected immediately after birth and NT-proBNP was measured via a human proBNP enzyme linked immunosorbant assay kit. Maternal liver function and fetal NT-proBNP measurements were log transformed and the relationship between them analysed using linear regression models adjusted for the potential confounding variables of labour induction, mode of delivery and gestational age at delivery. Figure 1 contains partial residual plots and fitted regression lines from the above models which include control participant data.

Results: A 1% increase in maternal TSBA or ALT concentration resulted in a 0.24% or 0.26% increase in fetal NT-proBNP concentration respectively ($p = 0.0367$ and $p = 0.0260$, Figures 1A and 1C). No significant associations were observed in women who had UDCA treatment ($p = 0.1355$ and $p = 0.2072$, respectively, Figures 1B and 1D). Maternal bilirubin values did not have any significant associations with fetal NT-proBNP concentration in untreated participants ($p = 0.1065$) or UDCA-treated participants ($p = 0.0646$).

Conclusion: Fetal NT-proBNP concentration in untreated ICP increases with increasing maternal concentrations of TSBA and ALT; this is not observed in UDCA-treated ICP. This suggests that pregnancies complicated by untreated ICP may have a higher likelihood of fetal impaired ventricular function which is associated with severity of disease. UDCA treatment appears to have a protective effect. Further studies are required to assess the clinical impact of these data.

FRI317

Penetrance, cancer incidence and survival of hemochromatosis in a long-term follow-up and epidemiological modelling study

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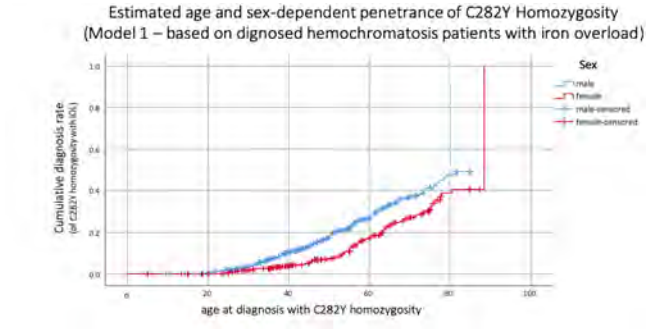
Background and Aims: Hereditary Hemochromatosis (HH) is associated with homozygosity for p.C282Y in *HFE* in 80% of patients, but disease penetrance occurs in only 14%, when HH is defined by presence of iron overload (IOL). Considering cirrhosis and hepatocellular carcinoma (HCC) as complications of HH, an even lower penetrance can be assumed, but the exact risk of this complications is unknown, especially in early diagnosed and treated patients.

The aim of the present study was to determine age- and sex-dependent penetrance of IOL in an epidemiological modelling study and assess the risk for cirrhosis and HCC during a long-term follow-up in a large cohort of HH patients from the geographical region of Tyrol in Austria.

Method: For this retrospective cohort study survival and cancer incidence data were extracted from national databases in 498 patients homozygous for p.C282Y between 1996 and 2018. HH was defined as homozygosity for p.C282Y and presence of provisional IOL (in males: Ferritin >300 + Transferrin saturation >50% and in females: Ferritin >200 + Transferrin saturation >45%) at the time of

genotyping. From the reported allele frequency of p.C282Y in the general population and the respective age distribution in Tyrol, an expected number of homozygous individuals was calculated. After correcting for mortality, age- and sex-specific estimates of disease penetrance were calculated based on patients diagnosed with HH and the expected number of homozygous individuals in 2008 and 2018. Crude incidence rates for HCC and prostate cancer as a control as well as survival status on 28 January 2019 were assessed to calculate age-standardized cancer incidence rates for HH patients and risk genotype carriers.

Results: Age- and sex-dependent estimates of HH penetrance for p.C282Y homozygous individuals are 28–40% in males and 18–25% in females aged 60 years or older (Figure). Among the 498 patients with homozygosity for p.C282Y, the crude penetrance estimate was 14% when only diagnosed patients alive with provisional IOL were considered in both sexes. In this group of p.C282Y homozygotes, 73% of patients presented with provisional IOL. Mean age at diagnosis of p.C282Y homozygotes was 47.8 years. In this group, the diagnosis of HCC was made in 5 patients, which represents an estimated risk for HCC of 1:60 by the age of 80. For comparison, in the general population from Tyrol the risk of having developed an HCC by the age of 80 is 1:77 in men and 1:333 in women. Hence, no increased HCC risk could be found in patients with p.C282Y homozygosity. Regression analysis shows that age and sex were independently associated with HH penetrance.



years of age	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89
numbers at risk (males)	851	777	700	584	461	332	199	109	39
diagnosis HH with IOL	0	3	21	38	32	31	24	12	1
numbers at risk (females)	713	640	567	475	391	302	191	112	36
diagnosis HH with IOL	0	0	9	10	11	27	20	10	2

Figure: (abstract: FRI317)

Conclusion: Considering age and sex allows for a more accurate prognosis of hemochromatosis penetrance among p.C282Y homozygotes. Overall, no increased mortality or risk for the development of HCC could be identified in this long-term follow-up and epidemiological modelling study.

FRI318

Prevalence and characteristics of cystic fibrosis associated-liver disease in a cohort of cystic fibrosis patients

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Background and Aims: Cystic fibrosis (CF) is the most common autosomal recessive disease in Caucasians and is caused by CF transmembrane conductance regulator (CFTR) gene mutation. CF-associated liver disease (CFLD) is the 3rd leading cause of death in CF patients. Its prevalence is controversial since the term CFLD is used to describe a wide range of manifestations. Therefore, it is important to distinguish CF-associated from CF-related liver disease. CFLD is thought to be a pediatric disorder although adult-onset CFLD (ad-CFLD) is being increasingly reported together with the arrival of new definition criteria using noninvasive liver fibrosis tests. We aim to determine the prevalence and characteristics of CFLD in a cohort of adult CF patients.

Method: We retrospectively studied a cohort of CF patients followed at our CF clinic. Inclusion criteria were age >18 years, a typical form of CF and at least 1 year of follow-up. We excluded pulmonary transplant patients. Data on baseline and CF characteristics were collected. CFLD was defined as having 2 out of 3 criteria: persistent elevation of transaminases and/or gamma-glutamyltransferase, abnormal ultrasound findings and/or abnormal transient elastography (cutoff >6.8 kPa). Noninvasive fibrosis markers were calculated in all CFLD patients. Ad-CFLD was defined as CFLD diagnosed >18 years. Severe CFLD (s-CFLD) was defined as CFLD with cirrhosis and/or portal hypertension.

Results: A total of 113 patients were included, median age was 29 years and 58 (51%) were male. Median age at CF diagnosis was 6 months, 17% had meconial ileus, 54% had deltaF508 homozygous mutation, and 83% had pancreatic exocrine insufficiency. Sixteen patients (14%) had isolated hepatic steatosis. Forty patients (35%) had CFLD including 28 (70%) male patients. Median age at CFLD diagnosis was 10 years. Twenty-one patients (19%) had s-CFLD with a median age of 13 years and median delay to s-CFLD diagnosis was 2 years. Two s-CFLD patients had nodular regenerative hyperplasia, 1 had hepatocellular carcinoma and 4 others underwent liver transplantation. Six patients (5.3%) had ad-CFLD with a median age of 42 years including 1 patient with s-CFLD.

Conclusion: Thirty-five percent of adult CF patients had CFLD in our cohort and 19% had s-CFLD. We used new definition criteria for CFLD and identified ad-CFLD in 6 patients. Better characterization of liver involvement in CF is crucial in order to better target medical care in this population.

FRI319

Liver cirrhosis development and value of transient elastography among a large cohort of Wilsońs disease patients with a long-term follow-up in Spain

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Background and Aims: Wilson's Disease(WD) is a rare congenital disorder of copper metabolism, with hepatic and neuropsychiatric symptoms. Due to its low prevalence(1/30.000), long-term follow up analysis of patients remains critical.

Method: Collaborative study of two Hospitals in Spain; retrospective evaluation of WD patients(clinical presentation, therapy and evolution). Acceptable therapeutical compliance was set in >80% of the planned doses. Variables were expressed in n(%); median (IQR_{25-75}); differences were assessed by T-test/U-Mann-Whitney (quantitative) or Chi-square (categorical) and statistical significance was considered if $p < 0.05$.

Results: One hundred and seven patients were included in the analysis after a median follow-up (FU) of 15 years. Age at diagnosis was 17 (12–29);55% were male. The main initial manifestation was ALT increase (55%) with ALT 92.5IU/L (41–178);11 cases (10.3%) already had liver cirrhosis (LC) at presentation. In 86.9% cases, WD diagnosis was established with Leipzig score ≥4 points. The most frequent phenotype was chronic liver disease (H2,72%);7 cases (6.5%) presented a fulminant liver presentation (H1) and required urgent liver transplantation (LT). The most common initial therapy was D-penicillamine (66.4%). During FU, treatment was modified in 49% of cases (due to adverse events 39.6%; protocol 26.4%; inefficacy 20.7%; other 13.3%); in most of cases (73.5%), chelator was replaced by zinc salts. Despite a good global compliance (65.4%) and ALT

normalization(57%), 21 patients(19.8%) developed LC during FU. LC development was not associated with initial therapy, changes in medication or worst adherence. Age at diagnosis was significantly higher in patients developing LC compared to non-LC [24.5 (11–34) vs 14.5 (12–24), p = 0.013]. The FU time in LC patients was significantly lower than in non-LC (9.3 vs 17.3, p < 0.01), due to higher rates of LT and death(31.3% and 15.6% in LC *vs*. 4.1% and 0% in non-LC) (p < 0.01). Transient elastography (TE) was available in 79 cases (73.8%) at a median time of 15 years; TE value was 6.1 (4.9–8.5) Kpa. TE was significantly higher among LC (9.1 Kpa) compared to non-LC (5.6 Kpa) (p < 0.01), but values for LC were lower than those reported for other liver diseases.

Conclusion: Progression to cirrhosis was significant in this large cohort of WD patients; a late diagnosis is associated with a worse prognosis. TE values in WD patients with LC were significantly lower than those established for other chronic liver diseases.

Nurses and Allied Health Professionals research hepatology

FRI320

Employment after liver transplantation and contributing factors

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Background and Aims: Employment is important after liver transplantation. It has a positive effect on physical and mental health of the patient. Work related problems are regularly observed and discussed during follow up transplantation care. The extent of this problem in Erasmus MC is unknown.
Therefore we explored the employment rate of post-liver transplant patients in Erasmus Medical Center Rotterdam, as well as the contributing factors in employment reintegration.
Method: A retrospective cross-sectional single center study was performed. Included were patients who receive outpatient follow up in Erasmus Medical Center, aged between 18 and 65 at time of transplantation, and transplanted between 2006 and 2017. The data was collected with a questionnaire and supplemented with clinical information. Factors for resuming work known from the literature included age, gender, education level, household, liver disease, severity of liver disease, physical health, quality of life (RAND-36) and employment before transplantation. These were compared between the working and non-working patients after liver transplantation.
Results: Of the 185/378 (response rate 48,9%) patients who completed the questionnaire, 50,8% were working after transplantation. Of those who did not work after transplantation 21,1% indicate a disability which does not allow them to work and 9,2% did not work, because they (almost) reached retirement age.
Significant independent factors of employment after transplantation are: employment before transplantation (p < 0.001), age (p < 0.001), education level (p < 0.001), liver disease etiology (p 0.002) and physical health (p < 0.001). In a multivariable regression model, pre-transplant employment is the only predictive factor determining if patients return to work.
Conclusion: In this study we found that half (50,8%) of the patients are working after liver transplantation. Factors that can be influenced need more attention. Interventions aimed at (maintaining) better physical health and maintaining work are advised. Multidisciplinary interventions for transplant patients are advised to focus on maintaining employment status in the period on the waiting list for transplantation and should continue throughout the post-transplant period.

FRI321

Development of a district general hospital liver nurse service for patients with acute and chronic liver conditions

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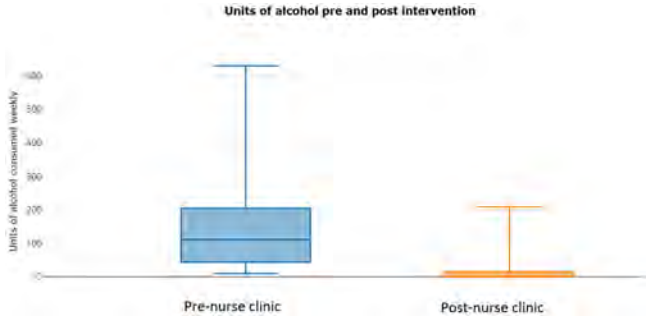
Background and Aims: Liver disease is the third largest cause of premature mortality in the United Kingdom (UK). This quality improvement (QI) aims to evidence the effectiveness of the liver nurse service (LNS), primarily out-patients with chronic liver disease (CLD), to improve quality of life and outcomes in line with NICE guidelines. Hillingdon Hospital is a district general hospital serving an ethnically diverse population of 300,000.
Method: Two liver clinical nurse specialists were recruited from the wards, trained in-house and iteratively developed the service with mentorship of the Consultant Hepatologist. Patient alcohol consumption was analysed using a Wilcoxon signed-rank test.
Results: Face to face nurse appointments increased from 278 in 2015/ 2016 financial year, to 1812 in 2018/ 2019, including FibroScan® clinics, whereby nurses provide health promotion and education. 200 FibroScans® were performed between 13/03/2019–19/08/19, most prevalent aetiology being non-alcoholic fatty liver disease (NAFLD) 33%. If patients were non-fibrotic, their referral pathway ended; avoiding consultant review. Telephone clinics were established in response to increased demand for follow up appointments in CLD patients, with 1013 telephone consultations in 2018/ 2019. Telephone clinics support admission avoidance and safe early discharge of liver patients, with remote blood monitoring, medication management and multidisciplinary team working. Alcohol dependent patients are offered holistic care with opportunity to be seen by alcohol assistant psychologists. Alcohol consumption data analysed for 72 patients demonstrated a significant decrease in weekly alcohol units consumed pre and six months post liver nurse clinic, reducing from a mean of 136 to 19.5 units (Z = –7.4, p < 0.001). 97% of patients reduced alcohol intake, 51% achieved abstinence. Nurses also provide a focus on bone health in CLD ensuring patients had DEXA scans in accordance to NICE guidelines. 115 scans performed between 2018 and 2019, 71% patients had low bone density, 79% of whom had cirrhosis.



Conclusion: This QI project has demonstrated how the LNS has been developed to provide a high quality service and holistic care for patients with liver disease. The service aims to provide further focus on inpatients helping to manage and co-ordinate care to improve patient outcomes.

FRI322

Managing decompensated cirrhosis – the importance of multidisciplinary engagement

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Background and Aims: Decompensated cirrhosis represents a paramount landmark in the disease progression of a cirrhotic. The index presentation of a decompensating event, or any subsequent decompensating event, requires swift investigation and management which can be guided by the "British Association for the Study of the Liver (BASL) Decompensated Cirrhosis Care Bundle". Many of the care items listed require support from the wider multidisciplinary team, however knowledge and utility of this care bundle may be limited within these groups. This qualitative study set out to determine the beliefs on managing decompensated cirrhosis held by members of the multidisciplinary team in a tertiary liver transplant unit in central London.
Method: A 10-point questionnaire mapped to individual care points within the BASL Decompensated Cirrhosis Care Bundle was created and distributed to members of the multidisciplinary team on a tertiary liver transplant unit. Following the questionnaire, interviews took place to discuss misconceptions/false beliefs regarding the care of decompensated cirrhosis and thematic analysis was performed. Post-hoc education was delivered where required.
Results: A total of 15 participants (uptake 100%) filled in the questionnaire and were interviewed: 7 were registered nurses (RNs), 6 junior doctors, 1 dietician, and 1 pharmacist. Thematic analysis revealed that, particularly amongst RNs, advanced liver disease was felt to be a contraindication to thromboprophylaxis in hospital. Another common misbelief seen in all participants aside from specialist-grade doctors was transfusion targets for gastrointestinal hemorrhage with most respondents targeting >90 g/L. A universal theme which was extracted from the interviews was that active involvement from multidisciplinary members of the team in delivering the BASL Decompensated Care Bundle would achieve higher real-world uptake, and help allied health professionals more readily identify sub-optimal standards of care, and thereby improve outcomes for our decompensated cirrhosis population.
Conclusion: The BASL Decompensated Cirrhosis Care Bundle should be delivered as front-line care with engagement from all members of the multidisciplinary team looking after these patients in order to deliver consistently high standards of care.

FRI323

The first step towards comprehensive nurse-led hepatology care: evolution of the Hull specialist liver nurse service (SLNS)

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Background and Aims: A specialist liver nursing service (SLNS) was launched in April 2018 to improve quality of care for patients with chronic liver disease (CLD) in our Trust.
Method: The SLNS was delivered by an experienced senior nurse and comprised: A new day-case paracentesis service, nurse-led clinics providing hepatoma surveillance and rapid post-discharge reviews, and daily nurse-led in-reach to the acute medical unit (AMU), emergency department and non-specialist wards to initiate early management (e.g. use of the BASL/BSG decompensated CLD care bundle) and identify patients for transfer to specialist ward or early discharge. The service was reviewed at 1 year to measure impact.
Results: Average length of stay (LOS) for paracentesis reduced by 94% to 5 hours, with 36% of drains now conducted as day cases, resulting in 416 saved bed days and financial savings of £166,400. It has also led to greater consideration of long-term drain placement in patients with end-stage disease, with 6 placed in 2018/19 vs 1 in preceding year. Nurse-led clinics have been very successful, with waiting time beyond planned follow up date for hepatoma surveillance significantly reduced from 71 to 13 days ($p < 0.001$); and 42% of patients discharged following decompensation having nurse rather than consultant review. Mean waiting time for post-discharge review was just 4.9 days, enabling safe earlier discharge from hospital. The SLNS is highly valued by non-specialist areas for timely and informative reviews, and use of the cirrhosis care bundle is now well-established. Crucially, all aspects of the service receive excellent feedback from both patients and colleagues. The immediate and significant impact of the SLNS on patient care contributed to the Trust giving approval for a new enhanced alcohol care team and recruitment of alcohol specialist nurses, to improve quality of care for these patients. Importantly however, the SLNS has now reached capacity and yet there are many more patients who could benefit from the service, as well as clear potential to broaden the nurse-led model of care into community hepatology. We have therefore submitted proposals for additional recruitment to support a multi-skilled and resilient SLNS working across our hospital and community.
Conclusion: The SLNS has improved care for patients with CLD. The service has been recognised as innovative locally, nationally and internationally, and laid the foundations for comprehensive nurse-led hepatology care for our patients.

FRI324

Prospective study of therapeutic education (TE) designed with a multidisciplinary team and participation of patients to improve the adherence to treatment of the patients and their quality of life (QOL)

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Background and Aims: Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease with variable severity and important consequences on the QoL. There is no specific study regarding therapeutic education (TE) for PBC. The association to other autoimmune hepato-biliary or extra-hepatic diseases and availability of new treatments strengthen the interest of TE.
Method: Prospective monocentric exploratory study of TE with a multidisciplinary team and patient participation aimed to improve the management of treatments and symptoms and the QoL of patients (pts) with PBC.
The participation/inclusion to the study was prospectively proposed during medical consultations in pts with PBC diagnostic criteria. The study was performed with a nurse experimented in TE and PBC care over one year. Questionnaires (QS) were given at each consultation (Month: 3,6,9,12): Analogic Visual scale (AVS) and PBC-40 score for the QoL, AVS and 5D-itch scale QS (analysis of Duration, Degree, Direction, Disability, Distribution within the 2 last weeks) for pruritus.
Results: 30/32 prospectively seen pts agreed to participate to the study (93,6%); 2 asymptomatic well-controlled pts denied (6,4%). The 30 included pts were 28 females/2 males (median 55 yrs). ***Baseline characteristics (number of pts):*** isolated PBC (n = 21), overlap syndrome with AIH (n = 9), extra-hepatic AI signs (n = 20); fibrosis: F0-F2 (n = 25), F3 (n = 2), cirrhosis (n = 3); pruritus (n = 2); treatment : UDCA (n = 25), fibrate (n = 6), budesonide (n = 4), azathioprine (n = 5). ***Adherence to the one-yr-TE-program*** : 26/30 pts (86.7%); lost of follow-up 4/30 (13.3%). ***New treatments after inclusion:*** UDCA (n = 2), obeticholic acid (n = 7), bezafibrate (n = 5). ***The effects of TE*** on the QoL and pruritus were analysed in the 26 pts who completed the whole study (Table 1).

Table 1: QoL and pruritus in the 26 pts who completed the study.

	Day 1	Month 12	P-value
QoL			
AVS mean/10	5.19	6.88	P = 0.0012
Improvement		19 (73.1%)	p = 0.004
Worsening		3 (11.5%)	
Stable		4 (15.4%)	
PBC-40 score	3.41	3.74	NS
Improvement		19 (73.1%)	p = 0.058 (NS)
Worsening		7 (26.9%)	
Pruritus			
AVS mean/10	3.42	1.27	P = 0.013
Improvement		12 (46.2%)	p = 0.044
Worsening		3 (11.5%)	
Stable		11 (42.3%)	
5D score (mean)	14.32	8.03	P = 0.025
Improvement		14 (53.8%)	p = 0.024
Worsening		3 (11.5%)	
Stable		9 (34.7%)	

This study was supported by a grant from the program Practice and Policy Program, Intercept, Canada.
The authors thank ALBI Association of patients for their help in the design of the study.

Conclusion: Patients with PBC exhibit a good adherence to a therapeutic education program which was associated with improvement in QoL and pruritus.

FRI325

Hepatitis B testing in Bcr-Abl tyrosine kinase inhibitor therapy

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Background and Aims: BCR-ABL TKIs are used in the treatment of haematological malignancies. An EU wide review found that in patients who are carriers of hepatitis B virus (HBV), reactivation can occur after receiving BCR-ABL TKIs. This may lead to acute liver failure resulting in liver transplantation or death. MHRA published guidance in April 2016 advising that all patients must be tested for HBV prior to starting BCR-ABL TKI therapy. All positive patients before and during treatment must be discussed with a hepatologist and all HBV carriers must be closely monitored during treatment for reactivation. The aim of this study was to investigate whether HBV screening takes place prior to, during and after stopping BCR-ABL TKIs and if practice has changed following the MHRA alert.

Method: All patients dispensed BCR-ABL TKIs from April to Sept 2019 from Royal Free London Hospitals were investigated. Using dispensing records, screening systems and clinic letters, treatment start dates were confirmed. Multiple hospital data sources were examined to determine if patients had a hepatitis B test prior to starting and during treatment. Data up to 10 years preceding treatment were analysed.

Results: A total of 50 patients received BCR ABL TKIs. The mean age was 47 years and M:F ratio was 30:20. The majority were on imatinib (64%) and no patients on ponatinib. The earliest start date was May 2010 and most recent was September 2019.

The table below shows the number of patients starting treatment before or after the MHRA alert and documentation of hepatitis B test prior to treatment.

Of 22 patients who had a documented HBV test prior to starting treatment, 1 patient was HBV core antibody (HbcAb) positive. This patient was monitored 3 monthly and remained HbcAb positive and HbsAg negative and was not given prophylactic HBV therapy. No other patients were retested post starting treatment.

	Total	Start date before MHRA alert n (%)	HBV test prior to treatment n (%)	Start date after MHRA alert n (%)	HBV test prior to treatment n (%)
Imatinib	32	9(28)	1	23(72)	10
Dasatinib	10	3(30)	2	7(70)	6
Nilotinib	7	6(86)	2	1(14)	1
Bosutinib	1	0(0)	0	1(100)	0
Ponatinib	0	0(0)	0	0(0)	0
Total	50	18(36)	5(28)	32(64)	17(53)

Conclusion: There was a 25% increase in HBV testing following the MHRA alert however testing rates remain low. Clinical pharmacists are well placed to prompt clinicians to order these tests as part of the clinical screening process for BCR-ABL TKIs.

FRI326

Impact of a nurse educational program for patient empowerment during sequential systemic therapy for hepatocellular carcinoma

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Background and Aims: The BCLC Nurse Educational Program (BCLC-NEP; Llarch, ILC 2019) was designed for educational purposes. This program reduced on-site visits, optimized health resources and secured patient compliance, although 26% of the unscheduled phone calls visits (UPCVs) received during the early phase of treatment (ePT), which includes the first 60 days of sorafenib initiation, were related to administrative tasks. Other systemic treatments such as lenvatinib, regorafenib, cabozantinib and ramucirumab also require dose adjustments within the first 60 days of starting treatment, and the safety profile of each treatment is slightly different. The aim of this study is to evaluate the impact of the BCLC-NEP on regorafenib-treated patients and analyze whether the rate of administrative consultations differs in the second line setting.

Method: This is a retrospective study in regorafenib-treated patients in Hospital Clinic of Barcelona from 08/2016 to 12/2018. The BCLC-NEP includes an on-site educational appointment before starting regorafenib, on-site visits every month and UPCV. We collected the number, causes, type of issues raised by patients and the solution offered by the nurse team. UPCVs were divided according to their timing (early or late (lPT) after treatment start.

Results: The nurses received 170 UPCVs from all (n = 21) but 1 patient who started regorafenib. We excluded 46 calls (27%) due to their administrative nature and 24 health-related UPCVs due to lack of information: We analyzed the remaining 100 UPCVs related to clinical issues; 42 calls from 19 patients were received in the ePT and 58 calls from 13 patients were received in the lPT. Analyzing the regorafenib related and non-related reported issues: the nurses solved 49 of the 100 UPCVs on their own.

Fifty-one of these 100 UPCVs were considered regorafenib related-adverse events (AE). All in all, the nurses themselves solved 14 (28%) of the regorafenib-related AEs during the ePT and 27 (54%) during the lPT.
Of all UPCVs received (n = 170), 58 occurred during the ePT and 9 (15.5%) were related to administrative issues. Interestingly, this shows a 10.5% reduction as compared to the sorafenib population.
Conclusion: The BCLC Nurses Educational Program implemented for regorafenib-treated patient clearly shows the relevant role of nurses in this population (54% reforafenib-related AE calls were solved by nurses during the late phase). The dose-adjustments needed in the early phase and previous experience with sorafenib influence the nature of the calls received. The use of this educational tool during the systemic treatment sequence suggest a progressive empowerment of the patients and a more efficient use of resources.

FRI327
Treatment with sorafenib on hepatocellular carcinoma –10 years' experience in a nursing-led outpatient clinic
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Background and Aims: Sorafenib has been the standard of care treatment for advanced hepatocellular carcinoma (HCC) since many years. Side-effects are common and often leads to dose adjustments or treatment withdrawal. Here, we investigated the results of a nursing-lead outpatient clinic focused on Sorafenib-treated patients with HCC. We aimed to describe treatment side-effects and the feasibility of the programme.
Method: Single-center study in Sweden. We included 210 patients treated with Sorafenib between 2007 and 2017. Retrospective chart review was performed to extract data on clinical characteristics, treatment side-effects and mortality.
Results: Mean age was 66.7 years, 76% were men and the most common cause of HCC was viral hepatitis (42%). Mean MELD score was 9.3. Median treatment duration was 29 weeks for the full study but was shortened between 2007 (median 34 weeks) to 2017 (25 weeks). Side effects were common and included nausea (45%), fatigue (30%), diarrhea (20%), hand-foot syndrome (22%), and other skin-related side-effects (18%). Dose adjustments were made by nurses in 97/210 patients (46%) with around 50% of the initial dose. Treatment withdrawal due to side-effects was uncommon (6/210, 2.9%) There was no reduction in annual mortality while on active treatment during the study period.
Conclusion: A Sorafenib treatment program run by specialized nurses was not associated with a reduced mortality during the study period and led to frequent dose-adjustments of treatment. Side-effects were very common and often lead to dose adjustments, but complete withdrawal was uncommon. This suggests that the program was efficient and safe and associated with a high tolerability in the treated population. Nursing-led outpatient clinics could be a safe and cost-effective method for patients with HCC.

FRI328
Pilot of an advanced liver disease nurse education program and its intersection with emerging models of advanced hepatology nursing practice
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Background and Aims: Advanced liver disease (ALD) and liver cancer are a growing public health issue. Burdensome treatments for Hepatitis C once consumed nursing resources. However, as new treatments shift Hepatitis C care from specialist to generalist practice, hepatology nurses are freed to diversify their skills to meet the growing burden of ALD and liver cancer. There are limited examples internationally of hepatology education programs that address and assess core ADL nurse capability.
Method: Phase 1 surveyed nurses' attitudes towards ALD training and identified their learning needs. This informed curriculum and assessments comprising nine months of formal hepatologist mentoring, face to face and online learning, hands-on skill development and clinical placement. Phase 2 evaluated relevance of, and satisfaction with the curriculum, nurse/hepatologist experience of mentorship, and local issues impacting course participation. Phase 3 used a descriptive, qualitative method. Analysis of semi-structured interviews with nurses and hepatologists was guided by Fawcett's nursing metaparadigm and Schuler's model of advanced practice.
Results: There was considerable demand for this program, which was rated as highly acceptable, feasible and relevant to ALD practice. Under mentorship, nurses developed education initiatives and local policies, and gave examples of nurse-led, patient-centred holistic models of advanced ALD practice. Participants revealed the *person* with ALD as socially disadvantaged, with substance use disorders and communication challenges. Their *health* embodied complex body needs. Their *environment* lacked ALD services, particularly in rural/regional settings, heightening stigma and discrimination. Emerging models of ALD *nursing* practice responded with listening to the whole story, being non-judgemental, being a lynch pin and building networks and lines of referral.
Conclusion: The program was acceptable, feasible and effective in building capability for advanced nursing practice. Further research could confirm the impact of education and advanced practice on ALD service access and outcomes.

FRI329
Diet lifestyle management of non-alcoholic fatty liver disease (NAFLD): a cross-sectional survey of clinicians
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Background and Aims: NAFLD is the most common liver disease in Europe, increasing in parallel with the obesity epidemic. Diet lifestyle intervention that induces weight loss (7–10%) prevents disease progression and is the standard of care recommended by International guidelines. We aimed to evaluate the status of diet lifestyle care for patients with NAFLD across Europe and Israel.
Method: In February-June 2019, clinicians with a NAFLD interest from 11 countries completed an e-survey to assess current practice and perceived barriers to the effective delivery of diet lifestyle interventions. Descriptive statistics and cross-tabulations were performed.
Results: 137 clinicians responded (86 gastroenterologists/hepatologists (GH), 31 dietitians/nutritionists (DN), 15 specialist trainees (ST) and 5 other); 50% specialist centres, 42% general hospitals and 8% primary care; mean age 42 years (range 25–69), 55% male. Two thirds responded that all patients with NAFLD would be eligible for diet lifestyle interventions. Despite this, 68% of respondents referred less than half their patients. Key barriers preventing referrals included no commissioned services (42%), short consultations/work overload (42%) and limited dietetic resources (32%). GH most frequently considered lack of services a barrier (50% vs. ST 27% vs. DN 23%) (p = 0.014). Access to multidisciplinary lifestyle services was reported by 23%; twice as many respondents from specialist centres used this option compared with general hospitals (31% vs. 14%) (p = 0.033).

Lifestyle advice delivered included impact of weight status on NAFLD outcomes (90%) and goal setting (64%) in brief/very brief interventions (43% vs. 34%). Only 52% advised weight loss of 7–10%. More DN and GH advised this target compared to ST (58% vs. 52% vs. 33%) (p = 0.003). Perceived obstacles to lifestyle advice delivery were short consultations/work overload (80%) and inadequate behavioural training (45%). More GH and ST reported inadequate training as an obstacle than DN (54% vs. 53% vs. 16%) (p = 0.001). Dietary approaches were face-to-face (94%) and Mediterranean diet (60%).

Conclusion: The survey highlights considerable variability in diet lifestyle care for NAFLD. Access to diet lifestyle interventions for eligible patients appears limited by a lack of commissioned services and resources. Given the high prevalence of obesity and NAFLD, these data suggest a need to improve training of clinicians to deliver diet lifestyle interventions.

FRI330

Development of clinical professional standards for liver transplant nursing

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Background and Aims: Nurses are the largest group of health care professionals and are intergral in making an impact on liver disease and providing quality care. Following the publication of the Royal College of Nursing (RCN) *Caring for people with liver disease: a competence framework for nursing* (2015); it was recognised that the area of liver transplant nursing was under represented. There were no professional clinical standards in liver transplant nursing to demonstrate competence or educational resources needed to develop this practice. New clinical professional standards were developed to promote consistency and person centred care delivery in both specialist transplant and referral hospitals in the United Kingdom (UK). The competence framework aims to benefit practitioners, employers, patients and the public by providing quality, safety and effectiveness of liver and liver transplant practice.

Method: Liver recipient transplant co-ordinators, transplant nurses and specialist nurses in referral hospitals across all liver transplant centers in the UK were involved in this development. The clinical professional standards cover the continuum of referral, assessment, listing for transplant and options for those not suitable for transplant. They describe high quality care pre-, peri- and post-liver transplant, as well as staying healthy in the long term. The standards were reviewed by previously identified stakeholders and final review completed with the original members of the development group.

Results: In September 2019 the RCN *Caring for people with liver disease including liver transplantation: a competence framework* was published. This is a refreshed and updated document that reflects contemporary person centred liver nursing practice as well as the new section on liver transplant nursing. The competence framework will be audited in two years' time to review the quality of care delivery, consistency of nursing care across liver transplant centres and the impact on patient experience. Future developments include benchmarking liver and transplant nursing practice against other European countries.

Conclusion: By developing clinical professional standards in liver and liver transplant nursing, care delivery can be benchmarked to ensure that nurses are delivering and patients are receiving high quality, evidence based, and effective person centred care.

FRI331

Nurse assisted follow-up after admission with decompensation in cirrhosis: a systematic review and meta-analysis

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Background and Aims: Liver cirrhosis is a grave disease with nearly half of the patients decompensated at diagnosis and substantial complications causing a high risk of admission and readmissions. Evidence supporting structured rehabilitation after admission with decompensation or complications to cirrhosis is scarce. This systematic review and meta-analysis aimed to evaluate the effects of nurse-facilitated interventions to prevent readmissions in cirrhosis.

Method: We searched MEDLINE, EMBASE, Web of Science; Cinahl databases through September 2019 for studies that evaluated a nurse-facilitated or nurse involved intervention instituted to benefit

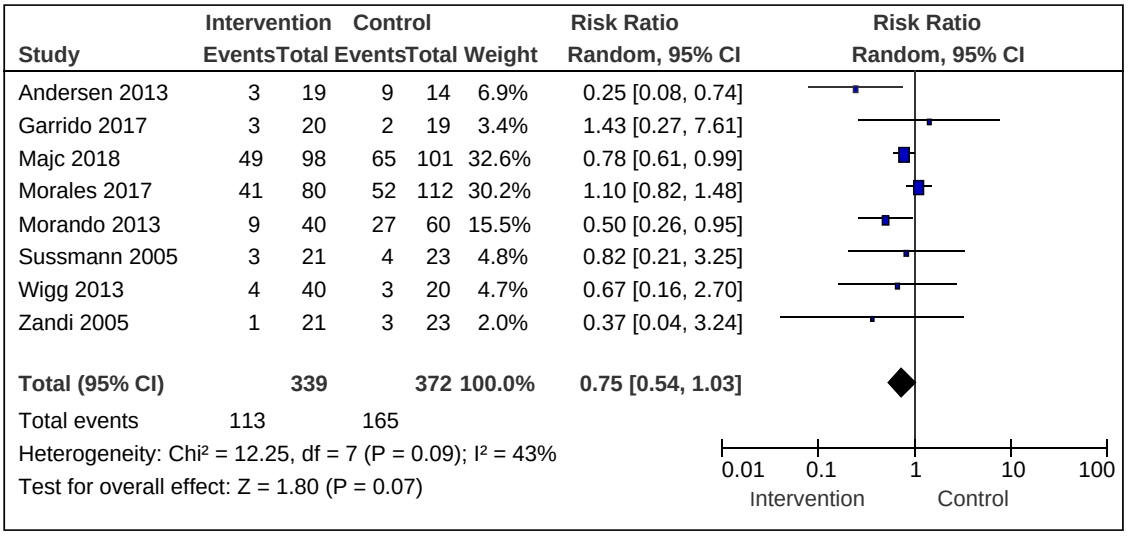

Figure: (abstract: FRI331)

the patients. Primary outcomes of meta-analysis were mortality and readmission. Secondary outcomes were patient education, self-management and patient perception of the interventions. Bias assessment of randomized trials and quality assessment of controlled and prospective trials were conducted to assess overall quality of the evidence.
Results: Ten controlled studies and five cohort studies comprising 1164 participants assessed educational, case-management and standard nurse-driven hospital follow-up interventions. Meta-analysis of eight studies comprising 711 participants revealed beneficial effects of interventions on mortality in fixed effects analysis, Risk Ratio 0.69, 95% CI 0.67–0.95, but the effect was insignificant in random effects analysis (Figure). Nurse assisted intervention improved readmission rates in fixed affects analysis (five studies, 436 participants), Risk Ratio 0.76, 95% CI 0.63–0.92, but was insignificant in random effects analysis (Figure). Evidence was of low quality and the heterogeneity was significant. In a qualitative review, all interventions increased participants' perception of disease and self-management.
Conclusion: Nurse facilitated interventions to prevent admission and readmissions in liver cirrhosis are well tolerated by patients and may be effective in prevention of mortality and readmission. Protocolled and clearly defined nursing interventions compared to structured standard of care are in demand.

FRI332
Prospective evaluation of a non-alcoholic fatty liver disease assessment pathway; impact of clinical nurse specialist role
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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is a major health burden, affecting 1 in 4 across the EU and is the commonest cause of abnormal LFTs in primary care. 60% of Irish adults are overweight or obese. While the majority of patients will not develop clinically significant liver disease, patients with fibrosis who may benefit from early specialist intervention remain undetected in the absence of a national NAFLD care pathway. The **aim** of this project was to develop a NAFLD screening pathway to identify patients with no/minimal fibrosis to be managed in primary care.
Method: Referrals with suspected and/or ultrasound evidence of fatty liver were triaged by the NAFLD nurse specialist to the NAFLD assessment clinic. Assessment included blood tests for chronic liver disease screen, NAFLD and FIB-4 scores, and Fibroscan examination. Following bimonthly MDT meetings, patients were discharged to primary referrer or retained in specialist care.
Results: From Jan-Oct 2019, 126 individuals (M:49%, F:51%, mean age 54 years, mean BMI 32.4 kg/m^2, 63% BMI>30 kg/m^2) were assessed. 85% of patients met diagnostic criteria for NAFLD. Of 126 fibroscans performed, 52% of patients had LSM < 7.0 kPa, 23% had LSM > 7.1 kPa <9.9 kPa, and 25% LSM > 9.9 kPa, and 52% of patients were eligible for discharge to primary referrer.
Conclusion: These data support the implementation of a NAFLD nurse specialist role to identify NAFLD patients for early specialist intervention.

FRI333
Illustrations supporting patient counseling before and after liver transplantation
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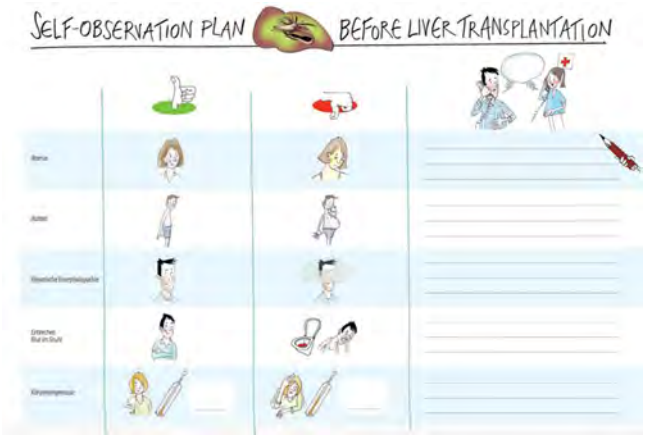
Background and Aims: Adherence to health relevant medical and behavioural recommendations before and after liver transplantation (LTx) improves clinical patient outcomes. Therefore, healthcare professionals should provide self-management support and education. Relying on oral counselling or written brochures only is sometimes challenging. We aimed to develop language-independent illustrations to support patient counselling before and after LTx.
Method: The participatory action research approach was led by two advanced practice nurses (APNs) and a nurse scientist. The interprofessional group from two liver clinics (5 nurses, 2 physicians) convened in two meetings and engaged in all four action research cycle phases: constructing, planning, acting, and evaluating. A professional illustrator participated in the second meeting.
Results: Constructing: In the first meeting, each participant presented three clinical practice situations in which illustrations would have facilitated patient counselling. Planning: All practice situations were discussed and three main themes for illustrations were identified: Understanding the disease (e.g. liver functioning), organizational aspects (e.g. preparing a hospital visit) and life after LTx (e.g. taking immunosuppressants, healthy behaviour). Acting: The illustrator presented four draft illustrations in the second meeting. The group used the "thinking aloud" technique to evaluate the drafts and discussed adaptations. The group agreed on a final set of twelve draft illustrations and two self-observation plans (fig. 1). Evaluation: To facilitate implementation, a group of additional healthcare professionals from both hospitals (n = 12) participated in cognitive debriefing interviews to evaluate the complete draft set using the "thinking aloud" technique. Overall, the drafts were clear and well accepted with high ratings in relevance and comprehensibility. However, it became obvious that the illustrations should not be a stand-alone tool, but must be integrated in counselling sessions provided by specialized liver nurses or physicians. The APNs finally tested the drafts during counselling and received good feedback from patients. Patients especially appreciated the visualization of complex relationships, which also helped them to better discuss and explain those issues with family members.



Conclusion: Early involvement of relevant stakeholders is key in practice development and the application of new tools. The detailed stakeholder and patient feedback was used to finalize the illustrations in view of specific content and layout. The illustrations have been implemented in patient counselling before and after LTx in both specialized liver clinics. This in turn, will hopefully not only improve counselling but also safety in deprived patient groups.
Astellas Pharma AG-financially supported the two meetings.

Immunology except viral hepatitis

FRI334
Soluble CEACAM1 induces regulatory T cells in vitro

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Background and Aims: CEACAM1 (carcinoembryonic antigen-related cell adhesion molecule 1) is a checkpoint regulator that controls T cell activation. CEACAM1 binds heteroligands, for example T cell immunoglobulin and mucin-domain containing-3 (TIM-3), or it acts as a homophilic adhesion molecule engaged in self-ligation. In mice, CEACAM1 promotes IL-2-dependent regulatory T cell (Treg) induction and -stability, and *Ceacam1*$^{-/-}$ mice exhibit exacerbation and persistence in murine immune-mediated hepatitis (Concanavalin A–induced hepatitis) resulting from an imbalance of effector T cells and poor Treg expansion and stability. Originally, CEACAM1 has been discovered as *biliary glycoprotein* that was detected as a soluble form in the circulation of human patients with autoimmune liver diseases, tumors of the gastrointestinal tract and cholestasis. However, an immune-regulatory role for soluble CEACAM1 (sCC1) has not been demonstrated so far. Here, we intend to study a putative immune regulatory role for soluble CEACAM1 in the induction of Tregs.
Method: sCC1 in sera from humans and mice was analyzed in Westerns Blots. In cocultures from bone-marrow derived, FACS-purified dendritic cells (DCs) and MACS-purified T cells from CEACAM1-deficient and WT mice, cytokine production was monitored using bead-based immunoassays and ELISAs. Cell-surface marker expression was characterized in flow cytometry. Phosphorylation of intracellular proteins after stimulation of T cells and T cells and DCs in cocultures with sCC1 was analyzed in flow cytometry and Western Blots.
Results: sCC1 is detectable in the circulation of patients with advanced primary sclerosing cholangitis (PSC) and is prominently found in sera of *mdr2*$^{-/-}$ mice. In cocultures of CD4$^+$ T cells and DCs, sCC1 binds to activated (CD4$^+$CD25$^+$ T cells) only, but not to naïve CD4$^+$ T cells. In CD4$^+$CD25$^+$ T cells, sCC1 induces phosphorylation of STAT5 (pSTAT5), and upregulation of Foxp3, and expression of Bcl-2. In CEACAM1-deficient CD4$^+$ T cells, reduction of pSTAT5 and Bcl-2 are observed. Furthermore, sCC1 inhibited production of IL-12 by DCs.
Conclusion: sCC1 binds to activated T cells in a homophilic and heterophilic manner and induces STAT5 signaling and Foxp3$^+$ Tregs. In T cell-DC cocultures, sCC1 supports IL-2 signaling on WT T cells and enhances their stability. This is the first report of the involvement of sCC1 in the induction of regulatory T cells. In addition, sCC1 appears to suppress DC-related IL-12 production via a yet unknown receptor.

FRI337
The alarmin IL-33 drives a ST2+ Treg-mediated anti-inflammatory immune response during immune-mediated hepatitis

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Background and Aims: Elevated levels of the alarmin IL-33 were shown in patients with chronic liver disease, indicating an immunomodulatory function of IL-33 in hepatic inflammation. In Concanavalin (Con)A-induced immune-mediated hepatitis, IL-33 was released by necrotic hepatocytes and induced immune responses by signaling through the IL-33 receptor ST2. We have shown previously that IL-33 pre-treatment protected from immune-mediated hepatitis, suggesting an immunosuppressive role of the IL-33/ST2 axis in liver disease. Since regulatory T cells (Tregs) expressing ST2 respond to IL-33, we aimed at investigating the IL-33-driven ST2$^+$ Treg response in the inflamed liver.
Method: To induce immune-mediated hepatitis, mice received ConA and were analyzed 24 hours later. To address the immunosuppressive effect of IL-33 on disease pathology, mice were treated with IL-33 on three days before ConA challenge. The phenotype of hepatic Tregs was determined by flow cytometry. Tregs from IL-33-treated FIR-tiger mice were adoptively transferred into C57BL/6 mice, which received ConA one day later.
Results: In homeostasis, the frequency of ST2$^+$ Foxp3$^+$ Tregs was elevated in the liver compared to the spleen. Hepatic ST2$^+$ Tregs expressed higher levels of Foxp3 than ST2$^-$ Tregs and the frequencies of ST2$^+$ Tregs expressing ICOS, KLRG1, Ki-67, CTLA-4, TIGIT, CD39, CD73, and IL-10 were increased, indicating an activated, proliferative and anti-inflammatory phenotype of this Treg subset in steady-state. In immune-mediated hepatitis, the frequency of ST2$^+$ Tregs was enhanced, which up-regulated expression of inhibitory molecules. Moreover, ST2-deficient mice developed more severe immune-mediated hepatitis despite an elevated frequency of Foxp3$^+$ Tregs in the inflamed liver, underlining the importance of the IL-33/ST2 axis for hepatic immune regulation. IL-33 pre-treatment before induction of hepatitis increased the frequency of activated hepatic ST2$^+$ Tregs compared to ConA-treated mice, which was associated with protection from liver disease. Moreover, transfer of IL-33-activated Tregs before ConA challenge potently suppressed immune-mediated hepatitis by inhibiting the inflammatory immune response.
Conclusion: The immune regulatory function of IL-33 in liver inflammation might be driven by expansion and recruitment of a highly immunosuppressive Treg subset expressing ST2.

FRI338
Plasmacytoid dendrtic cells protect against acute liver injury via IL-35

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Background and Aims: Plasmacytoid dendritic cells (pDCs) are well known as a subset of anti-viral immune cells that produce type I interferons. Recently, it has become clear that pDCs also have immune suppressive functions in various diseases of human and mice. However, the role of pDCs in liver diseases, especially non-viral liver diseases, remains largely unknown.
Method: A total 22 patients with acute hepatitis and 21 healthy controls were enrolled, and their peripheral blood (PB) and liver sections was used to analyze the frequency and phenotype of pDCs. In a mouse study, C57BL/6 male mice were administered Concanavalin A (ConA) to induce acute liver injury. The immune phenotype and function of specific subsets of immune cells in the PB and liver were evaluated by flow cytometry and IHC.
Results: We initially found that the number of CD123+ BDCA-2+ pDCs in the PB and liver of patients with acute liver failure, including acute-onset autoimmune hepatitis, was significantly reduced compared to that of healthy controls, suggesting a contribution of pDCs to the pathogenesis of acute hepatitis. We further examined the specific role of pDCs in liver injury using a ConA-induced immune-mediated acute hepatitis mouse model. In general, CCR9+ Siglec H+ PDCA-1+ pDCs were more abundant in the liver and small intestine (SI) than other organs in steady state, and hepatic pDCs dramatically decreased following ConA-induced acute liver injury. Depletion of pDCs in Siglec-H-DTR transgenic mice exacerbated the severity of liver inflammation compared to that in wild-type mice. Conversely, adoptive transfer of Flt-3L-induced pDCs, but not conventional DCs,

significantly suppressed liver injury. These results suggest a protective role for pDCs against ConA-induced acute liver injury. Mechanistically, the serum levels of IL-35, an IL-12 family regulatory cytokine, were significantly increased in pDC-transferred mice, and IL-35 neutralization canceled the suppressive effect of pDCs. Depletion of regulatory T (Treg) cells using anti-CD25 antibody also canceled the suppression of acute liver injury by systemic IL-35 upregulation by pDCs. Together, these results suggest that the suppressive effect of pDCs on acute liver injury is mediated by IL-35 through interactions with Treg cells. Furthermore, we found that CCR9 deficient pDCs unidirectionally migrated to the inflamed liver with less migration to SI and exert stronger suppression compared to wild-type pDCs.
Conclusion: pDCs play a substantial role in regulating acute liver injury via the IL-35 axis. Adoptive transfer of pDCs with CCR9 inhibition might be a novel therapeutic option for severe acute liver failure.

FRI339

Hepavac-101 first-in-man clinical trial of a multi-peptide-based vaccine for hepatocellular carcinoma

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Background and Aims: Hepatocellular carcinoma (HCC) is the third leading cause of death from cancer globally with an extremely variable 5-year survival rate. Immunotherapy strategies for HCC may represent a key therapeutic tool to improve clinical outcome in HCC patients. HepaVac-101 (EudraCT Number: 2015-003389-10; NCT03203005), is a single-arm, first-in-man Phase I/II clinical trial evaluating a therapeutic cancer vaccine in patients affected by HCC. It is a highly innovative, novel approach based on a multi-peptide vaccine (IMA970A) combined with an RNAdjuvant® (CV8102).
Method: The IMA970A *off-the-shelf* vaccine includes 5 HLA-A*24 and 7 HLA-A*02 as well as 4 HLA-DR restricted peptides identified and selected from native human HCC tumor tissue by applying the XPRESIDENT® discovery platform. CV8102 is a novel ribonucleic acid (RNA) based immunostimulatory agent inducing a balanced Th1/Th2 immune response.
HLA-A*02 and/or A*24-positive patients with very early, early and intermediate stage HCCs have been enrolled to be treated with 9 intradermal vaccinations consisting of IMA970A plus CV8102 following a single pre-vaccination infusion of low-dose cyclophosphamide acting as an immunomodulator. Study drugs are applied without concomitant anti-tumor therapy aiming to reduce the risk of tumor recurrence/progression in patients who have received all indicated treatments according to the standard of care and remain without evidence of active disease that warrants further treatment. The primary endpoints of the HepaVac-101 clinical trial are safety, tolerability, and immunogenicity. Secondary/exploratory endpoints are additional immunological parameters in blood, infiltrating T-lymphocytes in tumor tissue, biomarkers in blood and tissue, disease-free survival/progression-free survival and overall survival.
Results: Patients were enrolled in 6 centers located in 5 European countries i.e. Italy (Naples and Negrar/Varese), Germany (Tübingen), UK (Birmingham), Spain (Pamplona) and Belgium (Antwerp). 82 HCC patients have been screened for suitable HLA haplotypes, 22 patients were put on study treatment (i.e. received at least the pre-treatment with cyclophosphamide). So far, the observed safety profile is as expected. Immunogenicity data will be available at time of the meeting.
Conclusion: The HEPAVAC-101 clinical trial is the achievement of the HEPAVAC Consortium supported by the European Commission's 7th framework program with contract No. 602893 (www.hepavac.eu).

FRI340

High somatic mutation and neoantigen burden do not correlate with decreased progression-free survival in HCC patients

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Background and Aims: Cancer genome instability leads to accumulation of mutations which may result into tumor-specific mutated "neoantigens", not be affected by central T-cell tolerance. Such neoantigens are considered the optimal target for the patient's anti-tumor T cell immunity as well as for personalized cancer immunotherapy strategies. However, only a minor fraction of predicted neoantigens are relevant to the clinical outcome. A strategy for predicting mutated neoantigens relevant to survival in HCC patients is needed.
Method: In the present study, a prediction algorithm was applied using datasets of RNA sequencing from all 377 HCC patients available at The Cancer Genome Atlas **(TCGA),** to predict neoantigens to be presented by each patient's autologous HLA molecules. Training and validation sets were used to assess the validity of the analysis.
Results: Neither the somatic mutations nor the number nor the quality of the predicted neoantigens correlate as single parameter with survival of HCC patients who do not undergo immunotherapy treatment. Furthermore, the preferential presentation of such neoantigens in the context of one of the major MHC class I molecules does not have an impact on the survival. On the contrary, the expression of GZMA is significantly correlated with survival and, in the context of high GZMA, a direct correlation between number and quality of neoantigens with survival is observed.
Conclusion: This is in striking contrast to results described in cancer patients undergoing immunotherapy, in which a strong correlation between Tumor Mutational Burden, number of predicted neoantigens and survival has been reported (Mauriello et al., Cancers 2019).

FRI341

Myeloid derived suppressor cells enhance regulatory T cell suppressive activity via IL-10, iNOS and PDL-2 in cirrhotic patients with sepsis

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Background and Aims: Decompensated cirrhotic patients are more prone to bacterial infections leading to sepsis. Myeloid derived suppressor cells (MDSC) do expand in sepsis patients and correlate with ICU stay. However, their role in decompensated cirrhosis (DC) patients is not known. We studied the impact of MDSCs on T cells, suppressive Tregs and Th17 cells in decompensated cirrhosis patients with sepsis.

Method: Frequency of both monocytic and granulocytic MDSC (M and G-MDSCs), T-cells and Tregs was analysed in peripheral blood of DC patients with sepsis (Gr. A, n = 45), without sepsis (Gr. B, n = 20), and healthy controls (HC, [Gr. C, n = 10]). Expression of Naïve T-cell markers (CCR7+CD45RA+), T-cell exhaustion markers (PD-1 and TIM3), IL-10 on Tregs and HLA-DR on monocytes were analysed. mRNA levels of IL-10, iNOS, arginase-1, PDL-2 and PDL-1 were assessed in sorted MDSCs and monocytes. *Ex-vivo* co-culture of FACS sorted MDSCs and adherent monocytes with T-cells was assessed for proliferation and apoptosis using PI/ANNEXIN and CFSE. Ex-vivo co-cultured cells were also assessed for Foxp3 and IL-17 under Th0 and Th17 condition.

Results: Percentage of total and G-MDSCs were significantly higher in Gr. A than B (p = 0.005, p = 0.02) and C (p = 0.05, p = 0.02); though there was no difference in the M-MDSCs between groups. CD4+ T-cells were lower in Gr. A (p = 0.027) and B (p = 0.023) patients but with enhanced expression of CCR7+CD45RA+, PD-1 and TIM3 in Gr. A than C (p = 0.034, p = 0.009). The CD4+CD25+FOXP3+ Tregs were also higher in Gr. A (p = 0.041) and B (p = 0.047) compared to Gr. C. Expression of HLA-DR on monocytes was significantly low in Gr. A (p = 0.005) and B (p = 0.005) compared to HC. IL-10, iNOS and PDL-2 were found increased in MDSCs of Gr. A. *EX-vivo* cultured T cells with MDSCs in Gr. A patients showed suppression in proliferation and marked increase in ANNEXIN+ve cells compared to T-cells cultured with monocytes and also compared to Gr. B and C. Ex vivo cultured T cells with MDSCs under Th0 and Th17 condition showed increased expression of FOXP3+ (p = 0.028) in Gr. A compared to B and C.

Conclusion: Our results highlight the cross talk of MDSCs with T-cells inducing expression of FoxP3 in sepsis. MDSCs leads to the expansion of Tregs and enhanced immune suppressive as well as immune exhaustion environment through IL-10, iNOS and PDL-2 perpetuate sepsis in cirrhosis patients.

FRI342

Neutrophils are recruited at the periportal area in alcoholic liver disease and promote ductular reaction expansion

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Background and Aims: Alcoholic hepatitis is characterized by the expansion of ductular reaction (DR), which is accompanied by a prominent infiltration of neutrophils. Previous results from our group

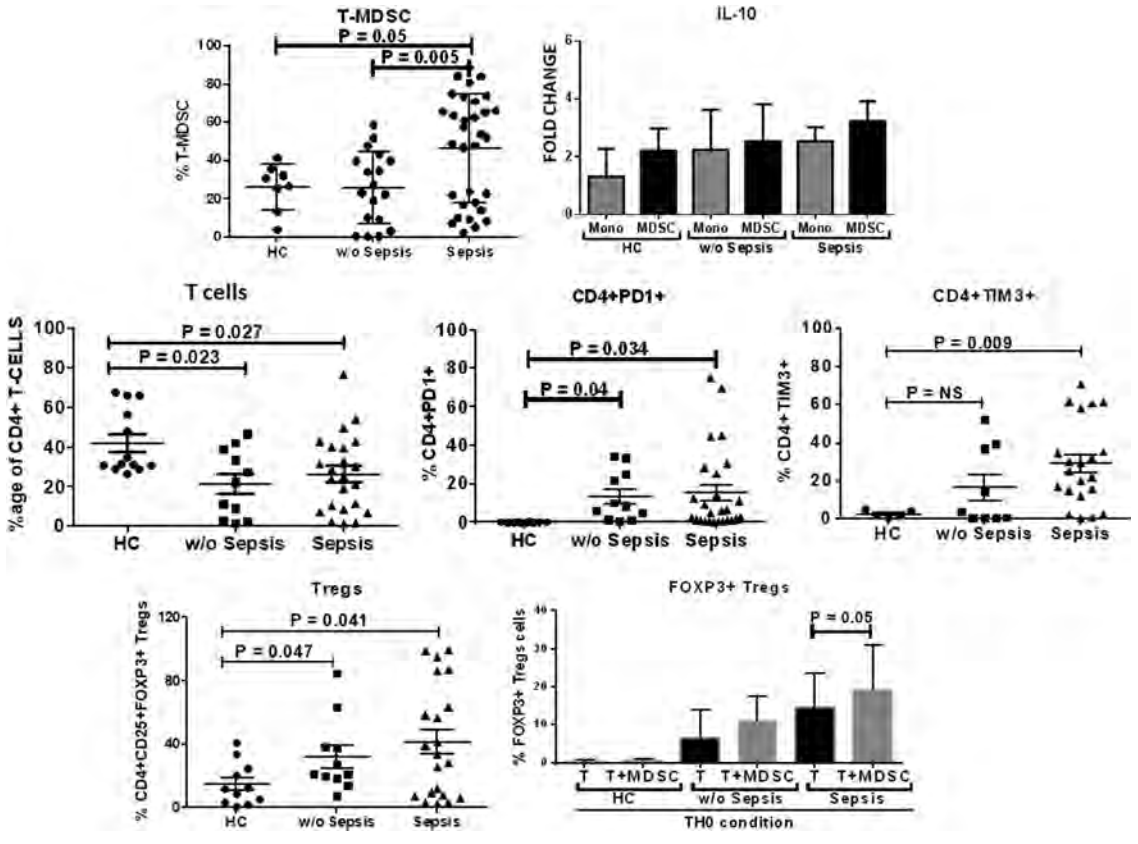

Figure: (abstract: FRI341)

revealed a proinflammatory profile of DR cells, suggesting their role in neutrophils recruitment to the periportal area. The aim of the present study was to investigate the recruitment of neutrophils around DR in chronic liver disease and explore their role in tissue repair.

Method: Infiltration of neutrophils was assessed by immunofluorescence and tissue clearing in stages of alcoholic liver disease progression. Intravital microscopy was performed in mice treated with DDC. Infiltrating mouse neutrophils were used for functional analysis by qPCR and FACS. In order to evaluate the impact of neutrophils on DR expansion, mice fed with DDC diet for 3 weeks were depleted of neutrophils by daily intraperitoneal administration of 1A8 antibody. Inhibition of neutrophil recruitment was performed by daily oral administration of CXCR1/2 receptor inhibitor.

Results: Histologically, DR was associated with neutrophil infiltration at the periportal area, as demonstrated in KRT7-MPO immunofluorescence. The number of infiltrating neutrophils increased with disease progression. Moreover, tissue clearing showed a direct contact of neutrophils with DR cells. Alongside, intravital microscopy in an experimental model of DR revealed a time-dependent infiltration of neutrophil, which were found in close contact with DR cells. Functionally, infiltrating neutrophils showed a lower phagocytic capacity and a reduced inflammatory response to LPS as compared with circulating neutrophils. Long-term inhibition of neutrophil recruitment with a CXCR1/2 inhibitor attenuated the expansion of DR and liver fibrosis. Likewise, treated animals showed a decreased hepatic gene expression of inflammatory markers fibrosis and DR. In addition, the chronic depletion of neutrophils by 1A8 antibody administration also showed a reduction in neutrophil recruitment and DR expansion both at histology and gene expression level.

Conclusion: Overall, our study shows that chronic liver disease progression is associated with increasing number of infiltrating neutrophils, which are found in close contact with DR cells. Infiltrating neutrophils show an altered functionality and their recruitment promote DR expansion. These results suggest that strategies targeting neutrophil recruitment may improve chronic liver injury.

FRI343

Obeticholic acid suppresses expansion of hepatic immune cell populations in a diet-induced obese and biopsy-confirmed model of non-alcoholic steatohepatitis

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Background and Aims: Both hepatic and extrahepatic inflammatory mechanisms are considered important components in the development and progression of non-alcoholic steatohepatitis (NASH). The present study aimed to profile liver and epididymal white adipose tissue (eWAT) leukocyte populations by flow cytometry following treatment with obeticholic acid (OCA), an FXR agonist currently in clinical development for NASH, in a diet-induced obese (DIO) and biopsy-confirmed mouse model of NASH with fibrosis.

Method: Male C57Bl/6J mice were fed the AMLN diet (40% fat, 20% fructose, 2% cholesterol) for 30 weeks prior to liver pre-biopsy sampling. Only animals with histology-proven steatosis (score ≥2) and fibrosis (stage ≥F1) were included and stratified into treatment groups. DIO-NASH mice received vehicle (PO, QD) or OCA (30 mg/kg, PO, QD) for 8 weeks. Vehicle-dosed chow-fed mice served as lean controls. Single cell suspensions from liver lobular and eWAT samples were stained with two panels of fluorescently labelled antibodies to detect and quantify leukocyte subsets, including monocytes/macrophages, neutrophils, T-cells, B-cells, Natural killer (NK) and NK T-cells, and analyzed by flow cytometry.

Results: DIO-NASH mice displayed significant increases in the total number of hepatic (~4-fold) and eWAT (~3-fold) leukocytes compared to chow-fed controls. Hepatic leukocyte expansion was dominated by Ly6C^{++} infiltrating pro-inflammatory monocytes and resident-like F4/80^{+} macrophages as well as a 5-fold increase in CD8^{+} T-cells/mg liver. In contrast, the increase in eWAT leukocyte populations in DIO-NASH mice reflected the tissue expansion, with only minor changes in the proportions of infiltrating leukocyte subsets. OCA significantly reduced the total number of leukocytes in the liver but had no effect in eWAT. The pronounced hepatic anti-inflammatory effects of OCA were primarily driven by >50% reduction in the number of infiltrating pro-inflammatory monocytes and CD8^{+} T-cells.

Conclusion: DIO-NASH mice showed distinct changes in liver- and eWAT-associated immune cell populations. Accordingly, changes in liver leukocyte populations were characterized by large expansions in both infiltrating and resident monocyte/macrophage subsets and CD8^{+} T-cells, whereas all major cell types in eWAT expanded to the same extent. OCA treatment led to distinct reductions in hepatic pro-inflammatory monocytes and lymphocyte populations, demonstrating the utility of flow cytometry to define anti-inflammatory mechanisms of compounds profiled for therapeutic effects in a DIO mouse model of biopsy-confirmed NASH mouse model.

FRI344

Drug screening against complement disorders using human stem cell-derived endothelium and liver organoids

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Background and Aims: The liver is a main source of complement factor secretion, whereas endothelial overactivation in alternative pathway leads to life-threatening diseases such as atypical Hemolytic Uremic Syndrome (aHUS). Working with human liver organoid (HLO) model, we found that HLO synthesizes high levels of functional complement factors. The present study leverages HLO-derived complement proteins to study complement dysregulation on human endothelial cells with a goal to interrogate aHUS pathogenesis.

Method: We first differentiated human induced pluripotent stem cell (iPSC) into both HLO and endothelial cells (ECs). Complement factor related gene expression and secretion of them from HLO were confirmed by transcriptome analysis and ELISA. The deposition of membrane attack complex (MAC), the final product of complement pathways, on iPSC-EC and its effect on cell injury were observed by supernatant of HLO after lipopolysaccharide (LPS) stimulation. Using this our novel MAC deposition system on iPSC-EC and conventional hemolysis assay, we conducted compound screening on MAC deposition. For in vivo evaluation, aHUS model, complement factor H W1206R mutant, mice was generated.

Results: For the first compound screening, we established high-throughput (HTS) 384 well-based in vitro soluble MAC ELISA assay. Using this HTS MAC ELISA and hemolysis assay, screening was conducted with over 35000 compounds. We identified 21 hit compounds. For the second screening, our original MAC deposition system on iPSC-EC was conducted. We identified several chemotypes of compounds which showed IC50 for MAC deposition around 1 μM in iPSC-EC. These compounds also significantly suppressed LDH release after complement over activation induced by LPS. For in vivo compound evaluation, the phenotypes of aHUS model mice were confirmed. They showed significant reduction of platelet numbers, increase of LDH levels in blood, kidney and liver fibrosis and thrombosis in multiple tissues like aHUS patient. One of our hit compounds significantly improved their aHUS phenotypes.

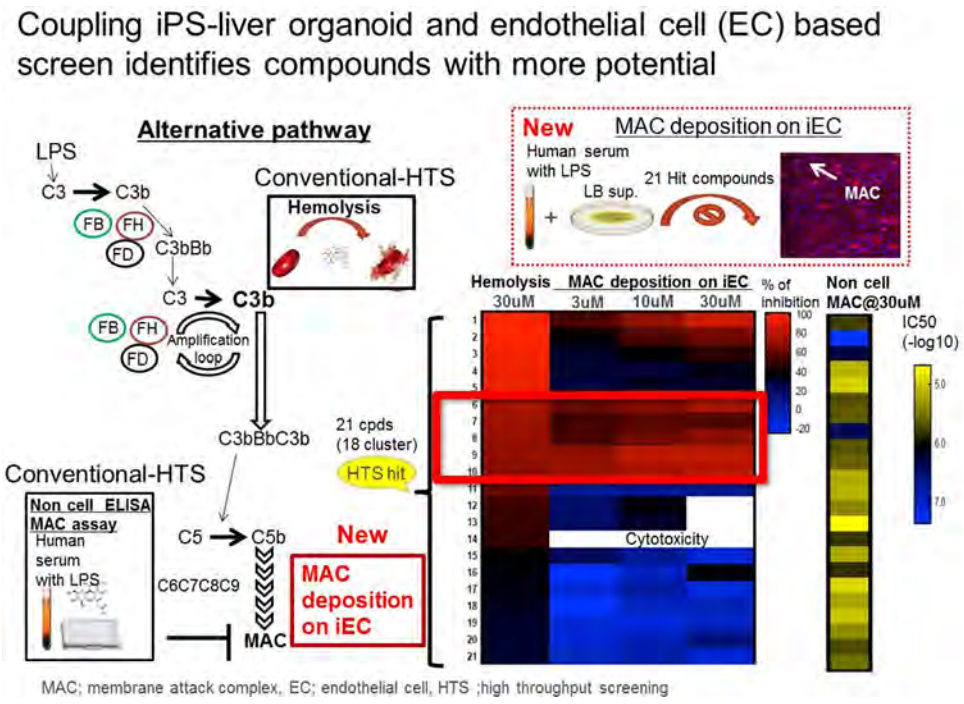

Figure: (abstract: FRI344)

Conclusion: Collectively, we developed new aHUS compound screening platform using iPSC-HLO and EC. Given that current approved therapy is limited to intravenous infusion of incredibly expensive monoclonal antibody, our approach paves the way to identify efficacious compounds against complement related diseases beyond current standard hemolysis screen assay.

FRI346

Immune cells restricted C/EBPbeta deficiency is associated with distorted hepatic mononuclear phagocytes composition, weight loss and spontaneous hepatitis

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Background and Aims: CCAAT-enhancer-binding proteins (or C/EBPs) are a family of transcription factors with a leucine zipper (bZIP) domain that are enriched in the liver. C/EBPbeta is a known regulator of numerous physiological and pathological conditions including the regulation of development and function of macrophages. Our aim was to investigate the importance of immune system C/EBPbeta expression in the liver at steady state.
Method: We have generated chimeric mice by injecting C/EBPbeta$^{-/-}$ vs. WT bone marrow into irradiated WT recipients. Mice were assessed for body and liver weight, biochemical profile for liver enzymes and bile acids, prevalence of hepatic mononuclear phagocytes cell subsets by flow cytometry analysis and qPCR of whole liver tissue for expression of genes associated with inflammation and fibrosis. In addition, we performed cell sorting of hepatic mononuclear phagocytes populations from C/EBPbeta deficient and proficient mice and conducted RNA-seq transcriptomic analysis of sorted populations.
Results: C/EBPbeta$^{-/-}$ recipient mice displayed lower body weight as compared to WT recipients. Serum levels of liver enzymes and total bile acids were increased in C/EBPbeta$^{-/-}$ recipients. Liver histology assessment revealed inflammatory infiltrates and tissue damage in C/EBPbeta$^{-/-}$ but not in WT recipients. Flow cytometry analysis of hepatic immune cell populations showed the absence of Ly6c^{low} monocytes and revealed significant decrease in cell numbers of Ly6c^{high} monocytes and Kupffer cells and an increase in monocyte-derived macrophages and CD11b^{positive} dendritic cells in C/EBPbeta$^{-/-}$ mice. RT-PCR analysis discovered significant elevation in relative expression of TNFα, IL6 and IL10 in livers of C/EBPbeta$^{-/-}$mice. RNA-seq analysis of sorted hepatic mononuclear phagocyte populations revealed 50 highly significant differential expressed genes between CEBPbeta deficient and WT hepatic mononuclear subsets that where especially prominent for the Ly6c^{high} monocytes population. Enriched biological pathways include among others regulation of immune system, inflammatory response and response to stimulus.
Conclusion: Great knowledge was obtained using C/EBPbeta$^{-/-}$ mouse model at different pathological conditions. Our data demonstrate vast abnormalities in the same model, already at the naïve like, steady state. Based on our findings, we suggest that previous C/EBPbeta$^{-/-}$ data should be re-challenged with this novel point of view.

Viral Hepatitis A, B, C, D, E: Immunology

FRI347

Platelet activation during chronic hepatitis B infection exacerbates liver inflammation and promotes fibrosis

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Background and Aims: Recurrent hepatitis activity during chronic hepatitis B virus infection (CHB) results in fibrosis and even hepatocellular carcinoma. It is still unclear what causes acute

exacerbation. As platelets have recently been identified a significant role in inflammation, we here investigated the role of platelets in mediating liver damage in patients with CHB.

Method: Platelet aggregation testing and flow cytometry were carried out to evaluate platelet activation status in 121 patients chronically infected with hepatitis B across different phases of the condition. The correlation between platelet aggregation rate and liver inflammation or liver fibrosis index was evaluated. To investigate the genesis of platelet activation, several serum cytokines were also assessed by MILLIPLEX microsphere-based multiplex cytokine assay.

Results: Active hepatitis patients showed a higher aggregation rate than others. Levels of CD62p, a marker of platelet activation, were also increased in this group of patients. Positive correlations between platelet aggregation rate and liver inflammation or liver fibrosis were also noted, indicating significant role of platelet in the progression of liver disease. The level of tumor necrosis factor alpha, which is known to trigger platelet activation, was markedly higher in the active hepatitis group ($p < 0.005$).

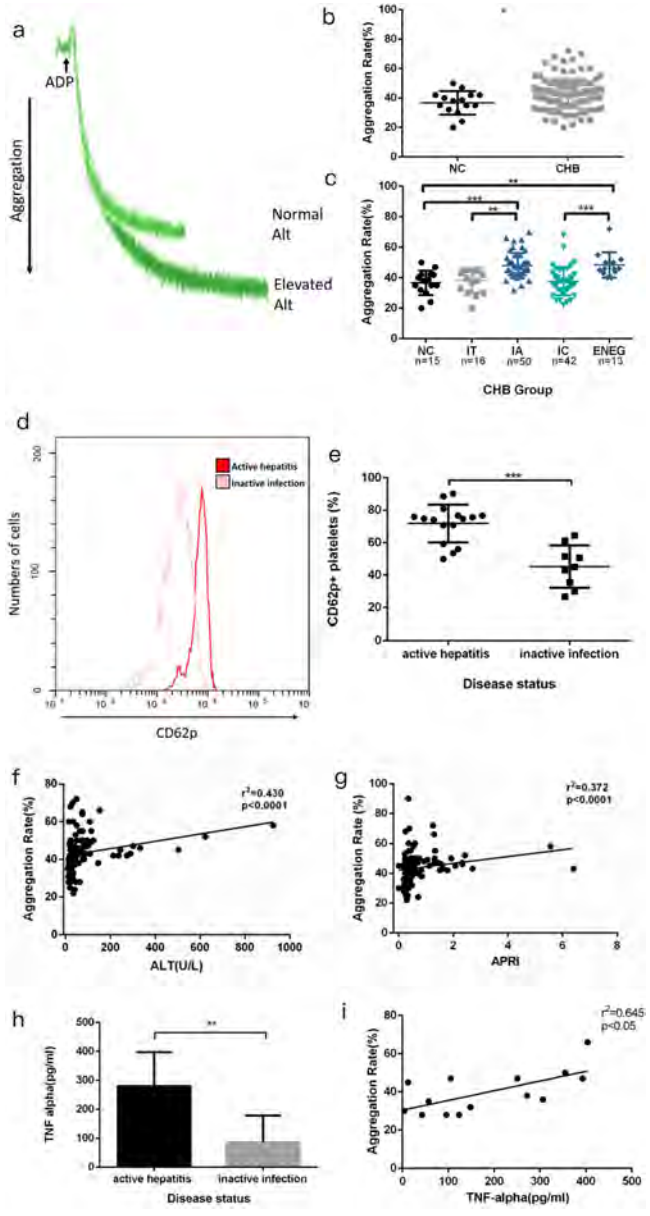

Figure: (abstract: FRI347)

Conclusion: Based on the findings in our study, platelet activation plays a vital role in the progression of CHB. Anti-platelet therapy may provide a new means of hepatitis B infection treatment.

FRI348

Entecavir-induced interferon-lambda 1 suppresses innate lymphoid cells 2 in patients with hepatitis B virus-related liver cirrhosis

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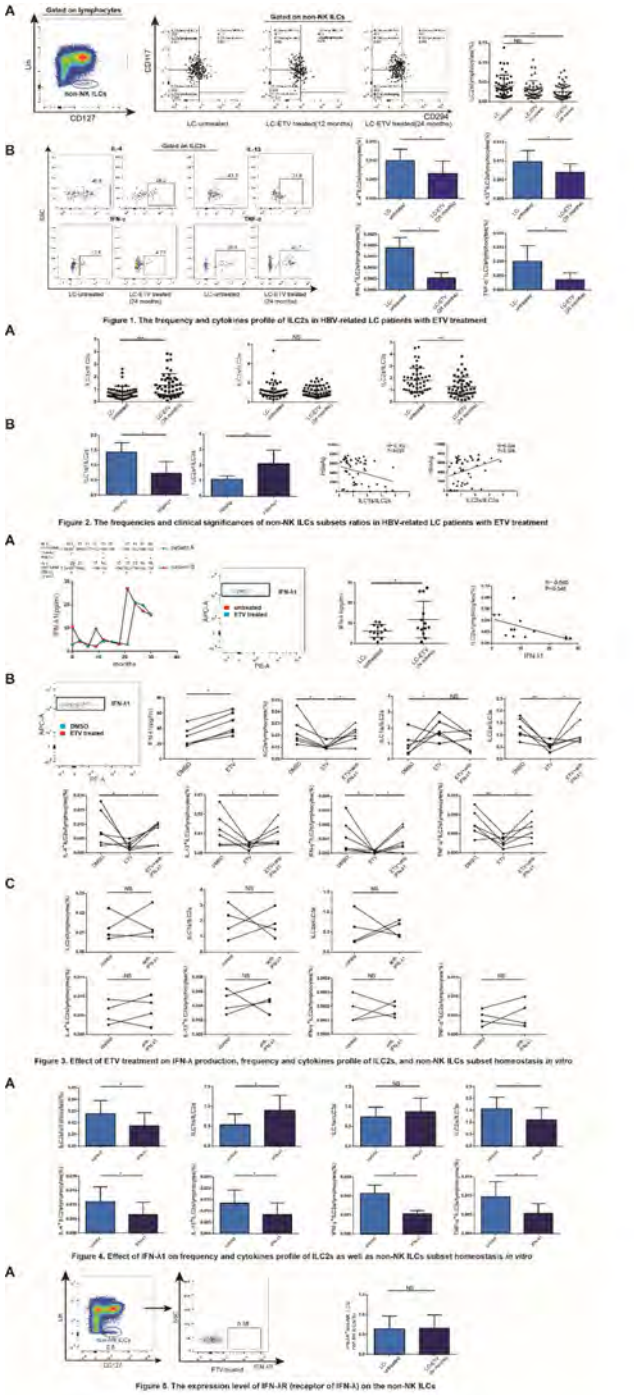
Background and Aims: Entecavir (ETV) is widely used for its effective suppression on hepatitis B virus (HBV) replication, and its influences on immune microenvironment are observed but not clearly understood. This study aims to explore the immunoregulatory roles of ETV on non-natural killer innate lymphoid cells (non-NK ILCs) in HBV-related liver disease progression.

Method: We enrolled treatment-naïve chronic hepatitis B (CHB) (n = 45) and HBV-related liver cirrhosis (LC) (n = 47) patients, and followed them with ETV treatment for 24 months. The frequency, correlation, and clinical significances of non-NK ILCs and their subsets in addition with cytokines profile of ILC2s were determined before and after ETV therapy. Interferon-lambda (IFN-lambda) levels were compared before and after treatment, and its correlations with ILC2s were identified in ETV-treated LC patients. The IFN-lambda level in supernatants, the frequency and intracellular cytokines production of ILC2s as well as non-NK ILCs subsets ratios were calculated after *in vitro* application of ETV, IFN-lambda 1 neutralizing antibody, or IFN-lambda 1 to peripheral blood mononuclear cells (PBMCs). Additionally, the expression level of IFN-lambda receptor on non-NK ILCs was detected.

Results: In LC rather than CHB cohort, compared with treatment-naïve patients, the frequency and cytokines production of ILC2s (IL-4, IL-13, IFN-gamma, TNF-alpha) decreased with increased ILC1s/ILC2s and decreased ILC2s/ILC3s ratio after 24-month ETV treatment. During treatment, hepatitis B virus e antigen (HBeAg) serological conversion group was characterized with higher ILC1s/ILC2s and lower ILC2s/ILC3s than no serological conversion group. ILC1s/ILC2s had negative and ILC2s/ILC3s had positive correlation with hepatitis B virus surface antigen (HBsAg) level. Furthermore, IFN-lambda 1, which increased with ETV administration, had negative correlation with ILC2s and influenced the non-NK ILCs homeostasis *in vitro* and *in vivo*. *In vitro* experiments showed that additional IFN-lambda 1 had same effects with ETV on suppressing ILC2 s, and in the presence of ETV, IFN-lambda 1 neutralizing antibody could increase the frequency and cytokines production of ILC2s. However, IFN-lambda receptor on non-NK ILCs of LC patients was barely detected regardless of ETV treatment.



Conclusion: ETV suppresses the frequency and cytokines profile of ILC2s through increasing IFN-lambda 1 production in HBV-related LC patients.

FRI349

A new therapeutic candidate vaccine can overcome hepatitis B virus-induced immune tolerance in a mouse model of chronic infection

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Background and Aims: Hepatitis B virus (HBV) infection is the leading cause of chronic liver disease and death worldwide representing severe public health concern. We have developed a novel vaccine regimen consisting in a prime-boost administration of ChAd155-hli-HBV (prime) and MVA-HBV (boost) viral vector vaccines, both encoding the hepatitis B core (HBc) and surface (HBs) antigens, followed by a recombinant protein vaccine containing HBc and HBs antigens adjuvanted with AS01 (HBc-HBs/AS01) administered either sequentially or concomitantly to the prime-boost.
Method: ELISA and Flow cytometry.
Results: The T-cell priming mediated by ChAd155-hli-HBV is enhanced by encoding of genetic adjuvant, hli. This vaccine regimen is intended to induce robust T-cells and antibodies against HBV antigens to overcome immune tolerance and to restore the immune control of HBV infection and ultimately to achieve hepatitis B functional cure, defined by loss of circulating HBs antigen, and sustained absence of HBV DNA detection. Our therapeutic HBV vaccine candidate has been tested in AAV-HBV *(adeno-associated virus expressing HBV genome)*-transduced HLA-A2/DR1 mice (transgenic for the human HLA-A2 and HLA-DR1 molecules). All AAV-HBV-transduced mice were positive for HBs antigen at 23 days post transduction and the HBs antigen concentrations were higher in sera from male than female HLA-A2/DR1 mice. Therefore, mice were randomized before vaccination according to both levels of HBs antigen and sex. The results showed that both tested vaccine regimens (*sequential or co-administration*) broke the tolerance established in this mouse model. The vaccine induced HBc- and HBs-specific $CD8^+$ T cell responses, as well as HBs-specific $CD4^+$ T cell responses in spleen and liver. In addition, high levels of HBc- and HBs-specific IgG responses were detected following the full vaccine regimens. We also evaluated inflammatory responses in the liver by measuring alanine and aspartate aminotransferase (ALAT and ASAT, respectively) levels in sera. These levels were not higher in sera from AAV-HBV-transduced and immunized mice than in sera from AAV-HBV-transduced non-vaccinated mice, suggesting the absence of liver-targeted cytotoxicity due to vaccination in this AAV-HBV-transduced mouse model.
Conclusion: Overall, the vaccine proved to be immunogenic despite the induced tolerance in this mouse model. These results strongly support the further clinical development of our vaccine candidates.

FRI350

Potential biomarkers of response in chronic hepatitis B patients who achieved HBeAg loss upon treatment with toll-like receptor 8 (TLR8) agonist selgantolimod

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Background and Aims: GS-US-389-2024 is a randomized, double-blinded, placebo-controlled Phase 2 study of selgantolimod, an oral selective small molecule agonist of TLR8 in virally suppressed CHB subjects on oral antivirals. Here we investigate potential biomarkers of HBeAg loss in CHB subjects after 24 weeks of selgantolimod treatment.
Method: Patients were randomized (2:2:1) to receive once weekly selgantolimod doses of 1.5 mg, 3 mg or placebo for 24 doses. Serum and peripheral blood mononuclear cells were collected at baseline and on-treatment and evaluated for soluble protein expression levels as well as proportions of myeloid, T-, B- and NK-cell subsets using multicolor flow cytometry. Association between HBeAg loss, biomarkers and clinical parameters was determined by regression analysis with generalized linear model and modular cytokine clustering.
Results: One HBeAg positive patient in the 1.5-mg dose group experienced HBeAg loss at week 12 of treatment and two in the 3-mg dose group at week 48 post-treatment. HBeAg loss was not associated with baseline viral parameters (ie. HBV-DNA, qHBsAg levels) or TLR8 SNP. Selgantolimod induced a dose-dependent increase of circulating

immune mediators such as interleukin (IL)-12, antiviral cytokines interferon (IFN)-γ, and various proinflammatory and anti-inflammatory cytokines (IL-1α, IL-1β, IL-6, and IL-1RA), peaking at 4 hours post-dose and returning to near baseline by 24 hours post-dose. HBeAg loss upon selgantolimod treatment was strongly associated with induction of VEGF [odds ratio (OR) 2.26, 95% confidence interval (CI) (1.56, 3.28); false discovery rate (FDR)-adjusted p-value = 3.1 × 10–4] as well as immune proteins IL-18 [OR 1.66 (1.19, 2.30); FDR = 0.016], CXCL7 [OR 1.74 (1.22, 2.50); FDR = 0.016], IL-12p40 [OR 1.73 (1.20, 2.51); FDR = 0.018] and eotaxin-1 [OR 1.51 (1.11, 2.24); FDR = 0.038]. Notably, selgantolimod induced a pronounced and progressive increase of IL-18 expression in HBeAg loss patients [median fold-change from baseline across all timepoints (IQR) = 1.32 (1, 1.55)] that was not observed in most other patients [1.01 (0.928, 1.22); Wilcoxon rank sum test p = 0.0034]. Transient expansion of CD4+CD57 +granzymeB+perforin+ T cells and CD57+ NK-cell subsets was also observed in these individuals. Studies are ongoing to determine the relationship between these immune cells and cytokine response.
Conclusion: Potential systemic biomarkers associated with TLR8 activation by selgantolimod were identified in CHB patients who achieved HBeAg loss. The biomarkers suggest a role for NK and cytolytic CD4+ T cells in TLR8 mediated immune response against HBV.

FRI351
Immunogenicity and efficacy of an HBV vaccine with an intrinsic checkpoint inhibitor
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Background and Aims: $CD8^+$ T-cells are critical for control of HBV infection, but their activity is hampered by low antigen immunogenicity and T-cell exhaustion. HSV-1 glycoprotein D (gD), when genetically expressed as a fusion protein with target antigens, serves as a checkpoint inhibitor of the B and T cell attenuator (BTLA)-herpes virus entry mediator (HVEM) pathway, which acts early during T cell activation. HSV-1 gD thereby augments antigen-driven $CD8^+$ T-cell responses. We describe the immunogenicity and antiviral activity of two distinct chimpanzee adenoviral vector (AdC) vaccines containing key HBV sequences fused into gD.
Method: Adenoviral vectors of chimpanzee serotypes AdC7 and AdC6 expressing three different HBV sequences, which are conserved between HBV strains and carry human T-cell epitopes, were generated in HEK 293 cells. Each vector was injected at different doses intramuscularly into different strains of mice – in some experiments mice were primed with AdC6 and boosted 6–8 weeks later with AdC7. Blood- or spleen-derived lymphocytes were tested 2–8 weeks after immunization for $CD8^+$ and $CD4^+$ T-cell responses upon a brief in vitro stimulation with peptide pools representing the HBV sequences and then stained for T-cell surface markers and intracellular IFN-gamma and analyzed by flow cytometry. Individual epitopes in different mouse strains were determined using peptide matrices. An adeno-associated virus (AAV) vector of serotype 8 expressing the 1.3 HBV genome was injected i.v. at doses ranging from 1×10^{10}–3×10^{11} genome copies (gc) into C57Bl/6 mice. Mice were vaccinated 4–8 weeks later or left untreated. HBV genome copies in serum were assessed before and after vaccination using a quantitative PCR.
Results: The vaccines were highly immunogenic and induced sustained T-cell responses. Multiple $CD8^+$ and $CD4^+$ epitopes were identified in different strains of mice including HLA-A2 transgenic mice. At low vaccine doses the response could be increased by a booster immunization with a heterologous AdC vector. Boosting furthermore increased the breadth of the T-cell responses. A single IM injection of the AdC6 vector produced sustained HBV DNA viral load declines of –2.0, –1.3 and –1.0 $\log_{10}$ mL through 8 weeks in animals injected with 1×10^{10}, 1×10^{11} and 1.5×10^{11} gc of AAV8-1.3HBV, respectively.
Conclusion: These HBV vaccines induced high immunogenicity and significant antiviral efficacy; a Phase 1b trial in HBV-infected patients is in development.

FRI352
Extracellular HBsAg clearance has minimal impact on CD8+ T cell responses in mouse models of HBV pathogenesis
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Background and Aims: During the course of natural hepatitis B virus (HBV) infection, the clearance of HBV surface antigen (HBsAg) by specific antibodies – a phenomenon referred to as seroconversion – is often associated with increased HBV-specific T cell responsiveness. Therefore, it is widely believed that therapeutic strategies aimed at reducing HBsAg may directly improve the antiviral potential of HBV-specific CD8+ T cells. However, a causative link between circulating, extracellular HBsAg and impairment of $CD8^+$ T cell function has not been definitely established.
Method: Here we used HBV replication-competent transgenic (HBV Tg) mice that were depleted of extracellular circulating HBsAg – via either spontaneous seroconversion or by treatment with therapeutic monoclonal antibodies – as recipients of HBV-specific $CD8^+$ T cells.
Results: Surprisingly, we found that circulating HBsAg had no impact on the capacity of HBV-specific effector CD8+ T cells to induce liver immunopathology. Moreover, depleting extracellular HBsAg had only minimal effect on the expansion of HBV-specific naïve CD8+ T cells undergoing hepatocellular antigen recognition and it did not alter their differentiation into dysfunctional cells. Finally, a brief exposure to circulating HBsAg did not affect the functional restoration of intrahepatically primed CD8+ T cells by interleukin (IL)-2-based immunotherapeutic strategies.
Conclusion: In summary, our results reveal that transient extracellular HBsAg clearance has minimal impact on HBV-specific CD8+ T cells responses and may have important implications for the treatment of chronic HBV infection.

FRI353
Analysis of regulatory T cells frequency and phenotype in chronic hepatitis C patients undergoing interferon-free therapies
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Background and Aims: Chronic hepatitis C infection has been associated with elevated frequency of CD4+ regulatory T (Treg) cells. High Treg cells count contributes to antiviral immunity inhibition and promotes liver fibrosis. Direct-acting antiviral (DAA) therapies achieve high rates of sustained virological response (SVR) regardless the degree of fibrosis/cirrhosis state. Since the liver plays a major role in maintaining immune system homeostasis, we hypothesize that liver cirrhosis per se may have an impact on Treg cells frequency and phenotype, even after SVR. The aim of this study was to characterize the potential changes of Treg cells in HCV-infected patients stratified by the fibrosis/cirrhosis state during and post DAA therapies.
Method: Frequency and phenotype of peripheral CD4 + CD25 + Foxp3+ Treg cells were analyzed by flow cytometry in HCV-infected patients with (n = 21) and without (n = 31) cirrhosis, at baseline, week 4 during therapy (W4) and, weeks 12 and 48 after the end-of-

therapy (FU12 and FU48, respectively). Samples obtained from 12 healthy individuals and 19 cirrhotic patients from other aetiologies served as controls.

Results: At baseline, the frequency of Treg cells in HCV patients with cirrhosis was elevated in comparison to healthy controls (mean 3.49% vs. 1.03%, p = .0023) and to HCV patients without cirrhosis (3.49% vs. 0.83%, p < 0.0001), but without statistically significant difference to that of cirrhotics non-HCV controls (3.49% vs 2.05%, p = ns). Longitudinal analysis revealed that Treg cells frequency did not normalize in HCV patients with cirrhosis even at FU48. Phenotypical analysis of Treg cells showed elevated expression of the CD45RO (memory) and HLA-DR (activation) markers in HCV patients regardless cirrhosis status at all time-points.

Conclusion: The elevated expression of CD45RO and HLA-DR in Treg cells of HCV patients, regardless cirrhosis status, indicate that HCV may leave a sustained imprint in Treg cells phenotype towards activation. However, elevated frequency was only detected in patients with cirrhosis, which also persists post DAA therapies. Thus, such immune system alterations associated with cirrhosis may impede immune system restoration and modulate the course of liver disease in these patients after HCV eradication.

FRI354

Characterization of the HBV-specific T cell pool reveals shared epitope usage but different phenotypes of HBV-reactive T cells across patients

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Background and Aims: Development of effective therapeutic strategies for HBV infection requires a better understanding of the nature and biology of CD8$^+$ T cell responses, including the epitopes driving the protective responses and the associated T cell phenotypes. HBV-specific T cell characteristics could be used as measure of clinical and biological activity of the candidate immunotherapy.

Method: Baseline and on-treatment PBMC samples from GS-US-330-1401, a study designed to evaluate the safety and efficacy of the T-cell vaccine GS-4774 in combination with Tenofovir Disoproxil Fumarate (TDF) in patients with chronic HBV infection were investigated by high-dimensional immune profiling. A mass cytometry-based highly multiplexed peptide-MHC (pMHC) tetramer staining strategy was applied to simultaneously screen over 100 HLA-A*11:01 and HLA-A*02:01-restricted HBV T cell candidate epitopes and to further phenotypically profile HBV-specific T cells in PBMC from HBV patients. Influenza- and EBV-specific CD8$^+$ T cells were tracked as controls and benchmarks in each sample. Peptide clusters were automatically generated grouping HBV peptide variants and virus-related epitopes. *Bona fide* antigen-specific T cells were identified by different objective statistical criteria, and phenotypes were assessed using high-dimensional analytical tools. Assessment of longitudinal changes in the HBV-specific CD8$^+$ T cell response and associations with clinical response were also performed.

Results: We detected HBV-specific CD8$^+$ T cells in the majority of patients analyzed as well as in longitudinal samples, with frequencies as low as 0.003% of the total CD8$^+$ T cell pool. Several epitopes were shared across patients including the previously reported epitopes HBV_{pol387} and $HBV_{core169}$. Phenotypes of HBV-specific T cells differed across patients and epitopes, with specific T cells ranging from naïve to terminally differentiated/exhausted profiles. Throughout the treatment period, no significant longitudinal changes in these phenotypes were observed among the patients evaluated. Correlations of measured parameters and clinical features and outcomes are ongoing.

Conclusion: The sensitivity and robustness of our antigen-specific T cell identification methodology enabled us to detect and profile rare HBV-specific CD8$^+$ T cells in a pilot trial cohort. The donor-dependent epitope reactivity and HBV-specific T cell phenotype provide insight into patient clinical history and/or outcome and may be leveraged as a biomarker to guide future HBV treatment strategies.

FRI355

Hepatitis B virus kinetics after nucleos(t)ide-analogue withdrawal in chronic HBeAg(-) hepatitis correlates with HBV-specific CD8+ response and HBsAg level

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Background and Aims: Nucleos(t)ide-analogue (NA) treatment controls HBV replication in chronic hepatitis B (CHB) eAg(−) but must be taken indefinitely. Persistent viral inhibition could decrease

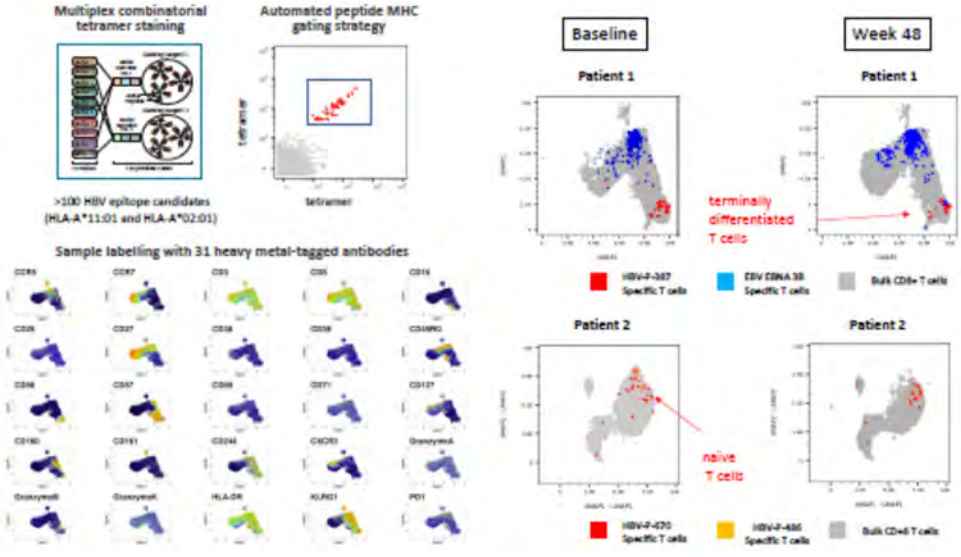

Figure: (abstract: FRI354)

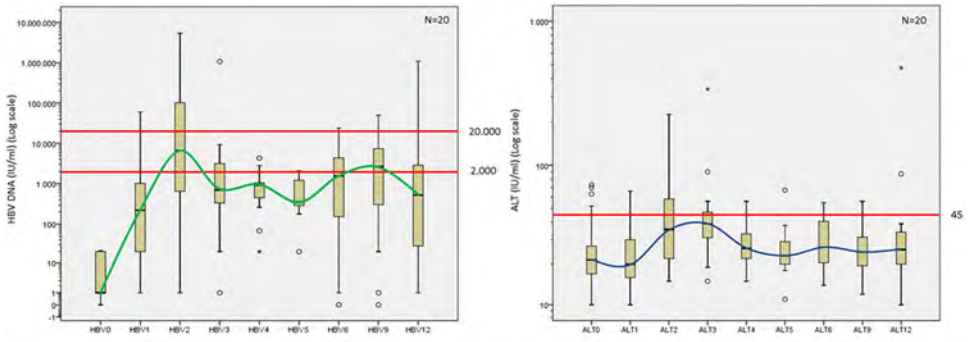

Fig. 1. HBV DNA and ALT dynamics during follow-up after NUC withdrawal in CHB eAg(-) cases with liver fibrosis <F3

Figure: (abstract: FRI355)

antigen load and favours adaptive immune response restoration and functional cure. The outcome after 12-month NA withdrawal was assessed. The role of HBsAg level and HBV-specific immune response was checked.

Method: 20 CHB eAg(−) cases with liver fibrosis <F3 and NA treatment duration >3.5 years were submitted to NA withdrawal. Patients were followed up for one year. Base-line ALT, HBV DNA and HBsAg level were tested. Monthly, HBV DNA and ALT, and quarterly, HBsAg was checked. In HLA-A2^{+} patients, base-line peripheral HBVcore$_{18\text{-}27}$ specific cytotoxic T lymphocytes (CTLs) were visualised directly ex-vivo and after specific proliferation by FACS analysis. After one-year follow-up, NA withdrawal outcome was assessed. Non-parametrical statistical analysis was carried out.

Results: During follow-up, nonpatient developed liver decompensation and only two flare-ups were detected without clinical consequences. Baseline HBsAg level negatively correlated with treatment duration ($r = -0.434$, $p < 0.05$). At month 2, a peak of HBV DNA level was observed (4.5 log, IQR 0.65) and it was followed by an ALT peak at month 3 (41 IU/mL, IQR: 35). At month 5, all cases had HBV DNA < 2000 IU/mL (2.6 log, IQR 0.6) and normal ALT (Fig. 1). At month 12, 60% of cases remained with HBV DNA < 2000 IU/ml, 30% <20.000 IU/mL and 15% had lost HBsAg; all of them with ALT into the normal range (Fig 1). HBV DNA level at month 12 positively correlated with baseline HBsAg ($r = 0.487$; $p < 0.05$). In fact, patients with baseline HBsAg <3.6 log had a lower HBV DNA at month 12 (<3.6log: 1.4 HBV DNA log[IQR: 2.16]; >3.6 log: 2.9 HBV DNA log[IQR: 1.4], $p < 0.05$) and more chance of HBsAg lost (<3.6log: 75%; >3.6 log: 0%, $p < 0.05$). Cases with HBsAg lost had a higher frequency of directly ex-vivo peripheral HBV core$_{18\text{-}27}$ specific CTLs out of total CD8 cells (HBsAg lost: 0.13%, HBsAg persistence: <0.02%, $p < 0.05$) and higher proliferation after specific in-vitro challenge (HBsAg lost: 30%, HBsAg persistence: <0.3%, $p = 0.08$).

Conclusion: NA withdrawal in non-advanced CHB eAg(-) is safe and leads to sustained virological response at month 12 in 90% of cases. Baseline HBsAg level negatively correlates with HBsAg lost and HBV DNA level at month 12. HBsAg lost positively correlates with a better HBV-specific CTL response.

FRI357

Hepatitis B virus-specific CXCR5+ CD8+ T cells may be related to hepatitis B virus clearance in chronic hepatitis B patients treated with pegylated interferon alpha

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Background and Aims: Hepatitis B virus (HBV)-specific CD8+ T cells are the main force in eliminating HBV, however, the functional exhaustion of HBV-specific CD8+ T cells impedes HBV clearance in chronic HBV infection. So, we studied a unique CD8+ T cell subset expressing C-X-C motif chemokine receptor 5 (CXCR5) in patients with chronic hepatitis B (CHB) in this study.

Method: A total of 38 CHB patients were enrolled in this study. Among them, Group A: 16 hepatitis B e antigen (HBeAg) positive CHB patients with alanine aminotransferase (ALT) >2 × upper limit of normal (ULN); Group B: 12 HBeAg positive CHB patients with ALT < 2 × ULN; Group C: 10 HBeAg negative CHB patients with ALT < 2 × ULN. In addition, eight of the 16 CHB patients in Group A were treated with pegylated interferon alpha (PEG-IFN-alpha). Frequency of HBV-specific CXCR5 + CD8+ T cells and levels of surface molecules in CXCR5 + CD8+ T cells were measured through flow cytometry.

Results: The frequencies of HBV-specific CXCR5 + CD8+ T cells were highest in Group A, followed by patients in Group B, and lowest in Group C. While the levels of surface molecules, inducible costimulatory molecule, programmed death 1, CD40 ligands and T cell immunoglobulin and mucin domain 3 were highest in Group A, followed by patients in Group C, and lowest in Group B. In addition, the levels of the four surface molecules were significantly higher in CXCR5 + CD8+ T cells than that in CXCR5-CD8+ T cells. In the longitudinal studies, after 12 weeks of PEG-IFN-alpha therapy, the frequency of HBV-specific CXCR5 + CD8+ T cells in patients whose HBV DNA level decreased by more than 3 log values showed an upward trend, while the frequency of HBV-specific CXCR5 + CD8+ T cells decreased at week 12 relative to baseline in the other patients.

Conclusion: Compared to CXCR5-CD8+ T cells, CXCR5 + CD8+ T cells exhibit partially exhausted in chronic HBV infection. However, HBV-specific CXCR5 + CD8+ T cells may be related to HBV clearance in CHB patients treated with PEG-IFN-alpha.

FRI358

Hepatitis B virus-specific CXCR5+ CD8+ T cells shows stronger functional activity in a mouse model of acute hepatitis B virus infection

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Background and Aims: Cellular immune response plays an important role in hepatitis B virus (HBV) clearance. This study aimed to discuss the functional status of HBV-specific CD8+ T cells expressing C-X-C motif chemokine receptor 5 (CXCR5) in a mouse model of acute HBV infection.

Method: The model of acute HBV infection was established by hydrodynamically transfecting female C57BL/6J (B6) mice with pCDNA3.1-HBV1.3 plasmids which contained a supergenomic HBV1.3-length transgene. The frequencies and phenotypes of splenic HBV-specific CXCR5+ and CXCR5-CD8+ T cells were assessed using flow cytometry. The splenic lymphocytes of transfected mice were isolated and stimulated by HBc-derived peptides overnight and then the cytokine secretion of HBV-specific CXCR5+ and CXCR5-CD8+ T cells were detected by flow cytometry.
Results: The frequency of HBV-specific CXCR5+CD8+ T cells increased from day 1 to day 4, and then decreased at day 7 and day 10 after transfection. And the levels of surface molecules, inducible costimulatory molecule (ICOS), programmed death 1 (PD1), CD40 ligands (CD40L) and T cell immunoglobulin and mucin domain 3 (TIM3) were significantly higher in HBV-specific CXCR5 + CD8+ T cells than that in HBV-specific CXCR5-CD8+ T cells at each timepoint. However, the expression of PD1 and TIM3 showed a gradual decline in HBV-specific CXCR5 + CD8+ T cells after plasmid injection, but increased in HBV-specific CXCR5-CD8+ T cells from day 1 to day 4. What's more, the secretion of interleukin-21 (IL-21), interferon gamma (IFN-gamma) and tumor necrosis factor alpha (TNF-alpha) after stimulated by HBc-derived peptides overnight were significantly higher in CXCR5 + CD8+ T cells than secreted in CXCR5-CD8+ T cells at each timepoint.
Conclusion: Although HBV-specific CXCR5 + CD8+ T cells are partially exhausted, it possesses a stronger cytotoxic function by producing high levels of HBV-specific IFN-gamma and TNF-alpha in acute HBV infection. Also, this cell subset may have the same function as follicular helper T cells in assisting humoral immune response by expressing ICOS and CD40L and secreting IL-21.

FRI359

Hepatitis D coinfection is associated with enhanced CXCR3 receptor expression of CD4 memory T cells and intrahepatic CXCR3 ligand expression compared to chronic hepatitis B patients

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Background and Aims: While the relevance of CXCR3+ CD4T cell memory subsets has been demonstrated in different HIV and HCV infection settings, the role of CXCR3 receptor/ligand axis in chronic hepatitis B (CHB) and D (CHD) virus infection is yet unknown.
Method: FACS multicolour panels determined the expression of chemokine receptors on PBMCs of 29 CHB, 27 CHD patients and 14 healthy individuals. Intrahepatic RNA levels of CXCR3 receptor and corresponding ligands were determined using human-specific Taqman RT-qPCR assays in cryopreserved liver specimens of 19 CHB, 29 CHD patients and 14 uninfected individuals, as well as in uninfected, HBV mono- and HBV/HDV co-infected livers of chimeric uPA/SCID/beige (USB) mice. Serum levels of chemokines were analysed in the sera of patients and USB mice by Bead Conjugation Assay.
Results: Median frequency of CXCR3 + CD4+ T cells was higher in CHD compared to CHB patients ($p < 0.0001$), while frequency of CXCR3+ NK and CD8T cells did not differ between hepatitis B and D patients. Subtype analysis revealed that CXCR3 + CD4+ T cells in CHD were mainly effector memory T cells (CD4 + CXCR3 + CD45RA-CCR7-, 68.4%) and subtype analysis showed significantly enhanced Th1 cell (CD4 + CD45RA-CXCR3 + CXCR5-, $p = 0.003$) but significantly reduced circulating T follicular helper cell (CD4 + CD45RA-CXCR3-CXCR5+, $p < 0.0001$) frequencies in CHD compared to CHB. Intrahepatic RNA analysis showed higher expression of both CXCR3 ($p = 0.0084$, 2.8-fold) and corresponding ligand chemokines CXCL9 ($p = 0.004$, 3.6-fold), CXCL10 ($p = 0.0028$, 2.2-fold) and CXCL11 ($p = 0.0056$, 2.1-fold) in CHD compared to CHB patients. In line with these patient data, also HBV/HDV co-infected livers of chimeric USB mice revealed significantly higher expression levels of human chemokines CXCL9, −10 and −11 compared to HBV mono-infected mouse livers (CXCL10: $p < 0.0001$, 7.8-fold; CXCL9: $p = 0.009$, 3-fold and CXCL11: $p = 0.0002$, 43.9-fold). Intriguingly, such differences in chemokine levels appeared less pronounced in serum. While CXCL10 levels were modestly higher in sera of CHD patients (1.7-fold, $p = 0.0073$) and HDV infected mice (4.1-fold, $p = 0.028$) compared to CHB patients and HBV infected mice, serum amounts of CXCL9 and −11 did not differ significantly either in patients or mice.
Conclusion: Peripheral TH1 polarized CXCR3+CD4+ T cells rather than serum chemokines mirror substantial differences between CHD and CHB regarding the intrahepatic expression of pro-inflammatory chemokines CXCL9-11.

FRI360

Magnitude and functionality of HEV-specific CD8+ and CD4+ T cell responses in asymptomatic blood donors resemble those in acute and symptomatic patients

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Background and Aims: Hepatitis E virus (HEV) infection is the main cause for acute viral hepatitis worldwide. In the large majority of immunocompetent individuals, HEV infection resolves asymptomatically, however severe courses with fulminant hepatitis and extrahepatic manifestations may occur. In order to clear infection an effective virus-specific CD4+ and CD8+ T-cell response is compulsory for other viral hepatitis viruses. For HEV infection, first evidence supports a critical role of HEV-specific CD4+ and CD8+ T-cell responses in order to achieve viral clearance. In acute symptomatic patients, elimination of HEV infection is accompanied by the occurrence of typical immune-related clinical symptoms such as fatigue, jaundice and ultimately, liver failure. The mechanisms of viral clearance in asymptomatic individuals with normal or only mildly elevated liver enzymes, however, remain obscure. In this study, we assessed the role of HEV-specific T-cell responses in asymptomatic infections without evidence for immunopathology.
Method: We comprehensively studied the HEV-specific CD8+ and CD4+ T-cell responses of 8 HEV RNA+ asymptomatic blood donors identified by routine screening of blood products with antigen-specific expansion, functional testing and pMHCI-tetramer stainings and compared them to a cohort of acute symptomatic HEV-infected patients.
Results: We identified functional and multi-specific CD4+ and CD8+ T-cell responses in all asymptomatic blood donors. In the 8 individuals, responses towards a total of 6 different HEV-specific CD8+ T-cell epitopes could be detected, that were restricted by HLA alleles HLA-A*02:01, B*07:02, and B*18:01. The 12 CD4+ T cell responses detected were restricted by HLA-DRB1*01:01 and DRB1*13:01. Magnitude and functionality of HEV-specific T-cell responses did not significantly differ between asymptomatic and symptomatic infections. Phenotypic characteristics of epitope-specific CD8+ T cells were also comparable in asymptomatic and symptomatic infections.
Conclusion: Our study found no difference between T-cell responses in symptomatic and asymptomatic HEV infections, implicating that

functional and multi-specific T-cell responses in HEV infection are not *per se* associated with immune-related pathogenesis. Why, in some cases, fulminant hepatitis occurs and whether this is caused by the HEV-specific T-cell response remains to be further elucidated.

FRI361

Peripheral soluble protein, transcriptomic, and methylation biomarkers associated with HBsAg loss in patients with chronic hepatitis B

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Background and Aims: Immune mechanisms accompanying the clinical response to IFN-α in chronic hepatitis B (CHB) have not been fully characterized. Here, we utilized transcriptome, DNA methylation and multiplex soluble protein profiling to characterize the differential signals associated with clinical response in pegylated interferon alpha-2a (PEG-IFN) treated CHB subjects.
Method: GS-US-174-0149 evaluated PEG-IFN alone or in combination with tenofovir disoproxil fumarate. Whole blood transcriptome and DNA methylation, and soluble plasma protein analysis were performed on baseline and on-treatment samples for study subjects with HBsAg loss (n = 14) and without HBsAg loss (n = 16). Gene expression signatures and methylation profiles were compared between the two response groups (HBsAg loss vs. no HBsAg loss). Association between HBsAg loss and magnitude of cytokine response was determined by regression analysis with Generalized Linear Model and modular cytokine clustering.
Results: Immune signature analysis identified dendritic cells, macrophages, monocytes, memory CD4T cells and CD66+ granulocytes in baseline samples (FDR<0.1) and enrichment of additional immune signatures, i.e. IFN-α and IFN-γ response, activated CD4, exhausted CD4 and CD8, effector memory and cytolytic CD8, and NK were significantly enhanced (FDR<0.1) at on-treatment timepoints for HBsAg loss subjects. A corresponding decrease in DNA methylation was detected for IFN-α (FDR = 5.34 e^{-13}) and IFN-γ (FDR = 5.76 e^{-9}) response genes on-treatment for only the HBsAg loss group. Peripheral proteins associated with IFN activity were increased at baseline in HBsAg loss subjects including IL-18 (p = 0.02) and IP-10 (p = 0.03). On treatment, levels of cytokines and chemokines were higher in the HBsAg loss group, though fold increases across both treatment arms were generally similar. Taken together, these results may signify a greater capacity of some CHB subjects to respond to immunomodulatory agents such as PEG-IFN.
Conclusion: Transcriptome, DNA methylation and soluble plasma protein analysis identified immune pathway differences between PEG-IFN-treated subjects that experience HBsAg loss compared to those that did not. These results inform the type of immune pathway alternations that may be needed for an effective clinical response.

FRI362

Tox expression on HBV-specific CD8+ T cells is linked to clinical stage of chronic HBV infection

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Background and Aims: T-cell exhaustion with dysfunctional effector responses towards virally infected cells is a hallmark of chronic HBV infection, but also observed in many other chronic infections. However, the mechanisms controlling the differentiation of exhausted T cells are poorly understood. Recently, the transcription factor and epigenetic modifier TOX was identified as a master regulator of the T-cell exhaustion program in mice. However, the role of TOX in T-cell responses to HBV and different human viral antigens remains unclear.
Method: To address this important question, we analyzed the phenotype and function of HLA-A*02:01 restricted virus-specific CD8+ T cells from 23 HBeAg negative and 7 HBeAg positive chronically HBV-infected patients, as well as patients chronically infected with HCV, HIV, and healthy controls using flow cytometry and high-parametric mass cytometry.
Results: We found that TOX expression on virus-specific CD8+ T cells was strongly increased in persistent viral infections. Interestingly, TOX was significantly higher expressed on HBV-specific T cells facing high levels of antigen isolated from HBeAg positive patients compared to patients with HBeAg negative infection (inactive carrier) indicating that TOX is linked to the different clinical stages of HBV infection and to high antigen load. In agreement with this assumption, we found that virus-specific CD8+ T cells obtained from chronically HCV- and HIV-infected patients with high viral loads also expressed high levels of TOX. Functional analysis linked TOX to a diminished polyfunctionality of exhausted HBV-specific CD8+ T cells suggesting a TOX-dependent programming of CD8+ T-cell dysfunction.
Despite these clear links of TOX to severe T-cell exhaustion, we also observed a high TOX expression on memory CD8+ T cells, in particular senescent cells with irreversible arrest of cell proliferation and cell function in patients with chronic viral infection but also healthy individuals. Indeed, differential patterns of Eomes, T-bet and TCF1 co-expression with TOX were transcriptionally linked to exhaustion vs. senescence programs.
Conclusion: In sum, these results reveal a context-dependent role for TOX tied into differential antigen-dependent exhaustion and senescence programs in humans. The links between TOX and differential exhaustion of HBV-specific T cells during different clinical stages of HBV infection has implications for immunotherapeutic approaches in chronic HBV infection.

FRI364

Distinct serum HBsAg levels show minimal effect on gene expression profiles of blood leukocyte subpopulations in non-viremic chronic HBV patients

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Background and Aims: Functional cure in patients chronically infected with hepatitis B virus (HBV) is a rare event, and long-term treatment with nucleoside-analogues (NUC) alone or in combination with interferon-based strategies do not improve rates. It has been postulated that viral proteins, such as hepatitis B surface antigen (HBsAg), have immunomodulatory activities and may negatively impact immunity to HBV. However, limited data is available to support the importance of HBsAg as an immunomodulator. Here we compared whole genome transcriptome profiles of purified blood leukocyte populations obtained from chronic HBV patients with highly distinct HBsAg levels.
Method: By means of multicolour flowcytometry (FACS) and microarray (GO Screen) both PBMC frequencies and FACS-sorted PBMC populations (CD4, CD8 and NKT cells, NK cells, B cells, dendritic cells and monocytes) were analyzed and transcriptionally profiled. We included a total of 24 IC patients and 16 NUC-treated patients with minimal HBV replication (HBV DNA max 2,250 IU/ml), normalized ALT, minimal fibrosis, and predominantly HBeAg-negative. Yet

they displayed a wide range of serum HBsAg levels (0.5–26,000 IU/ml). Patients were classified as high (average 8,912 IU/ml and 7,244 IU/ml serum HBsAg in IC and NUC-treated, respectively) and low (average 83 IU/ml and 151 IU/ml serum HBsAg in IC and NUC-treated, respectively).
Results: FACS analysis of the different leukocyte populations were comparable in patients with high and low levels of circulating HBsAg in IC and NUC-treated. Whereas significant differences in gene expression profiles were found between the various FACS-sorted cell populations, no to minimal transcript modulation was observed within each of these cell type populations in IC and NUC-treated patients with high versus low HBsAg levels. In particular, the largest modulation was observed in monocytes where only 0,16% of genes, out of the 20,251 covered in the array, were found to be tuned by HBsAg.
Conclusion: Our comprehensive approach revealed minimal effects of serum HBsAg levels on frequencies and gene expression profiles of peripheral leukocyte subpopulations in non-viremic chronic HBV patients. It cannot be excluded that HBsAg might impact the intrahepatic compartment where immune signatures are exacerbated.

FRI365
Hepatitis C virus chronicity is associated with a tox-1(high), Eomes(high), T-bet(dim) and PD1(high) phenotype of HCV-specific CD8+ T cells
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Background and Aims: First highly published studies have identified the expression of the "transcription factor thymocyte selection-associated high mobility group box protein" (Tox-1) in virus-specific T cells as central regulator of T cell exhaustion in chronic viral infection. Here, we analysed the immune checkpoint phenotype and intracellular transcription factor expression of virus-specific CD8+ T cells at different stages of hepatitis c virus (HCV) infection in order to identify possible roles of T-box transcription factor TBX21 (T-bet), Eomesodermin (Eomes), and Tox-1 for T cell exhaustion and outcome of HCV infection.
Method: HCV and FLU MHC class I tetramer-associated magnetic bead enrichment technique and 16-colour flow cytometry were performed with peripheral blood mononuclear cells (PBMC) of patients with acute (aHCV; n = 5), chronic (cHCV; n = 4) and spontaneously resolved (rHCV; n = 3) HCV infection and compared with PBMCs of healthy donors (HD; n = 5) to assess the expression of different immune checkpoint molecules and intracellular transcription factor profile of virus-specific CD8+ T cells.
Results: We observed a significant increase of T-bet(dim)Eomes(hi) HCV-specific CD8+ T cells at all stages of HCV disease compared with FLU-specific CD8+ T cells and a significant increase of T-bet(dim) Eomes(hi) HCV-specific CD8+ T cells in cHCV compared with rHCV ($p = 0.0078$) and aHCV ($p = 0.0171$) in this small, expanding cohort. Next, we analysed the expression of Eomes and Tox-1 at different stages of HCV infection. Here, we found a significant increase of Tox-1+ Eomes+ HCV-specific CD8+ T cells ($p = 0.0009$) and Tox-1(hi)Eomes (hi) ($p < 0.0001$) in cHCV compared to rHCV patients. We found a significant increase of Tox-1(hi)PD1(hi) HCV-specific CD8+ T cells during cHCV compared to rHCV and HD ($p < 0.0001$). Whereas rHCV showed a significant increase of Tox-1(low)PD1(dim) HCV-specific CD8+ T cells compared with cHCV ($p < 0.0001$).
Conclusion: Our results demonstrate a unique transcription factor expression signature during the chronic stage of HCV infection compared to patients who spontaneously clear the virus. In summary, we see that virus-specific CD8+ T cells in cHCV are Tox-1 (hi), Eomes(hi), T-bet(dim) and PD1(hi). Tox-1 and Eomes induction are associated with the exhaustion phenotype of HCV-specific CD8+ T cells in chronic HCV infection. Thus, the induction of Tox-1 and Eomes during the acute stage of infection might be early key events in the development of HCV chronicity.

FRI367
Profiles of expression of costimulatory molecules OX40 and OX40l in PBMCs and levels of soluble OX40/OX40l in plasma in chronic hepatitis B patients and health subjects
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Background and Aims: Recent studies suggested that the costimulatory molecules OX40/OX40L, members of the tumor necrosis factor (receptor) superfamily, play pivotal roles in regulating HBV immunity. Here, we report our comprehensive study results on the expression levels of membrane OX40 and OX40L (mOX40 and mOX40L) and levels of soluble OX40 and OX40L (sOX40 and sOX40L) in plasma in hepatitis B(CHB) patients and health subjects (adults and children).
Method: Peripheral bloods were collected from 52 CHB patients, 24 health adults and 13 health children. Expression of mOX40 in T cells and mOX40L in APCs were detected by flow cytometry. Levels of sOX40 and sOX40L in plasma were measured by ELISA. The results were analysed.
Results: While the expression of mOX40 on $CD3^+CD4^+$ and $CD3^+CD8^+$ T cells in PBMCs were significantly reduced in CHB patients compared with health adults, the expression of mOX40L on $CD3^-CD19^+$ B cells and $CD14^+$ monocytes as well as sOX40/sOX40L in plasma in CHB patients were significantly higher than that in health adults. Interestingly, among CHB patients, while negative correlations between levels of HBV DNA ($r = -0.574$, $p < 0.001$) and HBsAg ($r = -0.634$, $p < 0.001$) with the frequency of $CD3^+CD8^+OX40^+$ T cells were observed, there were positive correlations between the levels of HBV DNA ($r = 0.528$, $p = 0.001$) and HBsAg ($r = 0.346$, $p = 0.045$) with the frequency of $CD14^+OX40L^+$ monocytes. Additionally, we observed that $CD14^+OX40L^+$ monocytes and $CD3^-CD19^+OX40L^+$ B cells were both positively correlated with levels of ALT($r = 0.441$, $p = 0.004$; $r = 0.456$, $p = 0.002$, respectively), AST ($r = 0.472$, $p = 0.002$; $r = 0.531$, $p < 0.001$, respectively), ALP ($r = 0.416$, $p = 0.008$; $r = 0.599$, $p < 0.001$, respectively), GGT ($r = 0.421$, $p = 0.007$; $r = 0.499$, $p = 0.001$, respectively). Further, the levels of sOX40/sOX40L in plasma also had a significant positive correlation with HBV DNA, HBsAg, HBeAg, ALT, AST, GGT. Furthermore, we found that the levels of mOX40 expressed on $CD3^+CD4^+$ and $CD3^+CD8^+$ T cells, mOX40L expressed on $CD3^-CD19^+$ B cells and $CD14^+$ monocytes, as well as the level of sOX40 in plasma in health children were all significantly lower than that in health adults. Finally, the frequency of $CD3^+CD4^+OX40^+$ T cells was positively correlated with the age in health subjects including children and adults.

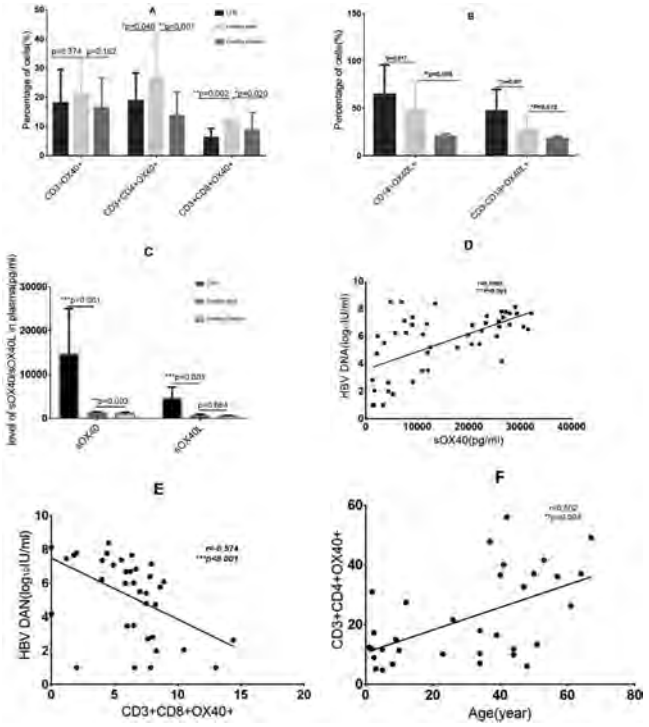

Figure: Frequency of mOX40+ and mOX40L+ cells and levels of sOX40 and sOX40L in CHB patients, health adults, and children.

Conclusion: These results suggest that the levels of cellular and soluble OX40/OX40L are both associated with the virologic status and pathogenesis of CHB patients, and therefore may be promising biomarkers for monitoring disease progression. Arguably, the reduced expression of OX40/OX40L in children suggests a vulnerable biological condition against HBV infection.

FRI368

Phenotypic variation among myeloid-derived suppressor cells (MDSC) in natural history phases of chronic HBV infection differentially impacts HBV-specific T cell response and homing: lack of functional normalization after anti-viral therapy

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Background and Aims: Chronic HBV infection (CHI) is associated with diverse natural history that includes Immune-tolerant (IT), HBeAg-positive chronic hepatitis B (CHB) (EP-CHB), inactive carrier (IC) and HBeAg-negative CHB (EN-CHB) phases. A hallmark of CHI is HBV-specific T cell dysfunction that is mediated by multiple regulatory mechanisms and the nature of response is influenced by the disease phases. Myeloid-derived suppressor cells (MDSC) have emerged as key regulator of T cell and their properties are sculpted by the microenvironment. Here, we investigated the distinctive features of MDSC in various phases *of* CHI, the factors responsible for their functional discrepancies and the impact of diverse phenotypes of MDSC on the response pattern and homing of HBV-specific $CD8^+$/$CD4^+$T cells. Effect of Tenofovir on MDSC profile and T cell response was also assessed.
Method: Flow cytometry, ELISA, cell-sorting and co-culture assays were performed.
Results: MDSC in EP-/EN-CHB patients showed profound suppressive ability, expressing Arg1, iNOS, PD-L1, CTLA-4 and CD40 at significantly greater levels relative to healthy controls (HC). However, in IT, only Arg^+MDSC and in IC, $iNOS^+$ and $PD\text{-}L1^+$MDSC were markedly higher than HC and comparable to CHB. Correlation analysis indicated that high HBsAg titer in IT and CHB was associated with elevated Arg^+MDSC, whereas high serum IL-1β (in CHB/IC) and TNF-α (only in CHB) potentiated PD-L1/iNOS and CD40/CTLA-4 expression respectively on MDSC. Further, HBV-specific IFN-γ^+ and IL-2^+ $CD8^+$/$CD4^+$T cells were significantly high in IT as compared to CHB and IC, while the homing receptor, CCR5 was poorly expressed on T cells of IT and CHB than IC. To test whether diverse phenotypes of MDSC could reciprocally regulate HBV-specific T cell response, HLA-DR^-CD33^+-MDSC sorted from patients in different disease phases, were co-cultured with autologous T cells in presence of overlapping peptides of HBV core protein. MDSC from CHB/IC, greatly attenuated IL-2 and IFN-γ production by HBV-specific $CD8^+$/$CD4^+$T cells, the effect being more pronounced in CHB. In contrast, MDSC of IT minimally affected the cytokine production by T cells. However, MDSC from IT and CHB downregulated CCR5 on HBV-specific T cells and disrupted trafficking of these cells. Addition of Arg1 or iNOS inhibitor during co-culture restored only HBV-specific IFN-γ^+T cells while neutralizing PD-L1 recovered both IL-2 and IFN-γ producing abilities of T cells, implying PD-L1/PD-1 signalling to be the key MDSC-mediated immunosuppressive mechanism in CHI. One year of Tenofovir therapy failed to normalize MDSC phenotype, serum IL-1β/TNF-α/HBsAg levels and T cell functions despite reduction in HBV DNA.
Conclusion: Diversity of MDSC during CHI impacts HBV-specific T cell response and homing. Hence therapeutic targeting of MDSC could boost anti-HBV immunity.

FRI369

Integrated analysis of serum immunological biomarkers in patients with chronic hepatitis C upon direct-acting antiviral treatment

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Background and Aims: The knowledge of timing of immune response remodeling upon DAAs can provide relevant evidences to support novel fields of clinical investigation. Important issues related to post-treatment has been recently raised. We sought to analyze the kinetics profiles of serum chemokines, pro-inflammatory/regulatory cytokines and growth factor in patients with chronic hepatitis C upon DDAs treatment.
Method: Fifty HCV patients, 33/50 (66%) males, mean age of 61 years (40–81 years), were enrolled in a longitudinal investigation carried out before (Baseline), during (2–4 and 8–12 weeks) and post-treatment (12–24 weeks) with sofosbuvir and daclatasvir or simeprevir. All patients had SVR. Serum biomarkers CXCL8, CCL11, CCL3, CCL4, CCL2, CCL5, CXCL10, IL-1β, IL-6, TNF-α, IL-12, IFN-γ, IL-15, IL-17, IL-1Ra, IL-4, IL-5, IL-9, IL-10, IL-13, FGF-basic, PDGF, VEGF, G-CSF, GM-CSF, IL-7 and IL-2 were quantified by Luminex™ platform. Twenty uninfected blood donors were control group (NI). Mann-Whitney test was used for comparison between HCV and NI groups and Kruskal-Wallis test for multiple comparisons followed by Dunn's post-test for sequential pairwise comparisons. The significance was considered at $p \leq 0.05$. The Prism GraphPad 8.0 software was used for statistical analysis and graphical arts. The study was approved by UFMG and FIOCRUZ-Minas ethical boards. All participants signed consent form.
Results: A clear biomarker storm was observed in HCV patients at the pre-treatment period, characterized by a massive increase levels of chemokines (CXCL8, CCL11, CCL3, CCL2, CXCL10), pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, IL-12, IFN-γ, IL-17) and growth factors (FGF-basic, PDGF, GM-CSF, IL-7) with minor increase in regulatory cytokines (IL-9, IL-13) as compared to NI. The kinetics of baseline fold changes monitored during and after DAAs treatment revealed a early

decline in the levels of CXCL8, CCL4, IL-6, IL-15, IL-17, IL-9, GM-CSF and IL-7 observed at 8–12 weeks of treatment, and a later remodeling of CCL3, CCL2, CCL5, IL1β, TNF-α, IL-12, IFN-γ, IL1-Ra, IL-4, IL-10, IL-13, PDGF, VEGF, G-CSF that reached lower levels at 12–24 weeks post-treatment. Higher ALT levels (>69 mg/dL UNL) and compensated cirrhosis at baseline were factors related to delayed immune response as compared to the rapid immune remodeling observed in patients with lower ALT levels (<69 mg/dL) and non-cirrhotic status.

Conclusion: The HCV treatment with DAAs resulted in a clear remodeling of the serum biomarker storm, hallmark of untreated HCV patients. Regardless the SVR response observed in all patients, the kinetics of serum biomarkers during and after DDAs treatment was associated with the pre-treatment high ALT and cirrhosis status. These findings added novel evidences for the immunological remodeling process triggered by DDAs.

FRI370

Higher proportion of responders with hepatitis B antibody levels ≥ 100 miu/ml with the trivalent HepB vaccine, Sci-B-Vac, compared to Engerix-B: results from the phase 3 double-blind, randomized study comparing immunogenicity and safety (PROTECT)

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Background and Aims: Sci-B-Vac®, a trivalent HepB vaccine with pre-S1/pre-S2/S antigens, may enhance immunogenicity in adults, compared to the monovalent (s-only) HepB vaccine, Engerix B®. HepB antibody (Ab) level >10 mIU/mL is accepted as a correlate of seroprotection (SPR), but higher levels (≥100 mIU/mL) and/or higher HepB Ab geometric mean concentration (GMC) may indicate a more robust immune response and be associated with longer duration of protection. The aim of PROTECT (Clinical Trials ID: NCT03393754) was to compare the immunogenicity and safety of a 3-dose regimen between Sci-B-Vac® and Engerix B® in adults.

Method: In a multinational, comparator-controlled, randomized, and double-blind study, 1607 adults in stable health (≥18 years, 80% ≥45 years), received either Sci-B-Vac® 10 µg or Engerix B® 20 µg, on days 0, 28, and 168. Immunogenicity, including SPR (% participants with HepB Ab level ≥10 mIU/mL), and safety outcomes were followed to day 336. Co-primary objectives were 1) non-inferiority of SPR in adults ≥18 years and 2) superiority of SPR in adults ≥45 years, 4 weeks after the 3rd dose. GMC and HepB Ab ≥100 mIU/mL were exploratory outcomes. GMC ratio was the fold change in GMC of Sci-B-Vac® compared to that of Engerix B®.

Results: Sci-B-Vac® was non-inferior to Engerix B® in participants ≥18 years old (SPR 91.4% *vs*. 76.5%) and superior in participants ≥45 years old (SPR 89.4% *vs*. 73.1%). The proportion of participants who achieved HepB Ab level ≥100 mIU/mL was 80.8% with Sci-B-Vac® compared to 60.7% with Engerix B® in adults ≥18 years (difference 20.1% [95% CI: 15.5,24.6%]), and 77.9% with Sci-B-Vac® compared to 56.5% with Engerix B® in adults ≥45 years old (difference 21.45% [95% CI: 16.2,26.6%]. The proportion of participants with HepB Ab level ≥100 mIU/mL was higher with Sci-B-Vac® compared to Engerix B® in key subgroups with co-morbidities, including BMI >30 (79.6% *vs*. 55.5%), current smokers (70.7% *vs*. 54.7%), and diabetics (59.3% *vs*. 45.0%). Sci-B-Vac® was well-tolerated with no safety signals with low rates of serious adverse events (SAEs) reported (Engerix B®: 2.6% and Sci-B-Vac®: 4.0%).

Conclusion: Sci-B-Vac® yielded a more robust immune response, reflected in high GMC ratios, compared to Engerix B® and met both co-primary immunogenicity endpoints—non-inferiority in adults ≥18 years and superiority in adults ≥45 years. Safety and tolerability were consistent with the known profile of Sci-B-Vac®.

FRI371

Hepatocyte-derived l-carnitine impedes HBsAg clearance in chronic HBV infection

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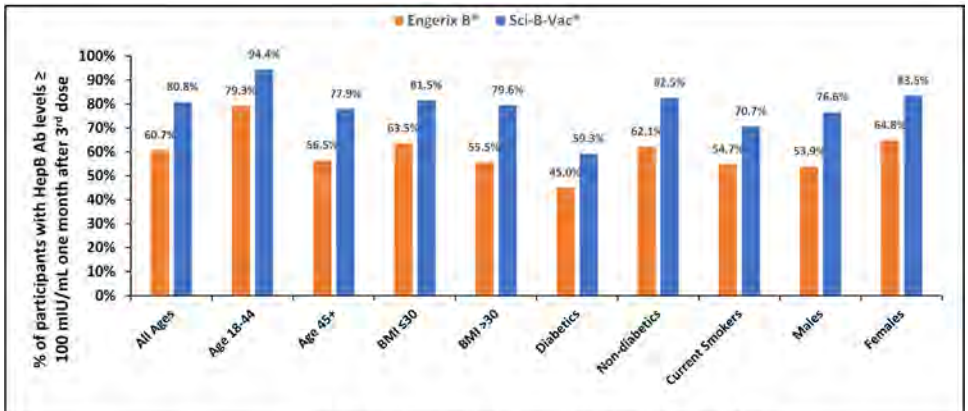
Background and Aims: The seroclearance of HBsAg is regarded as a functional cure of chronic HBV infection. An association between low levels of plasma L-carnitine (L-Cn) and treatment-induced HBsAg



	HepB Ab Geometric Mean Concentration one month after 3rd dose									
Engerix B®	192.616	720.591	142.28	260.916	109.979	41.297	221.419	161.88	106.603	273.477
Sci-B-Vac®	1148.224	4570.377	858.16	1343.013	883.965	222.34	1312.236	449.44	761.009	1498.189
GMC Ratio	6X	6.3X	6X	5.1X	8X	5.4X	5.9X	2.8X	7.1X	5.5X

Figure: (abstract: FRI370)

Figure:

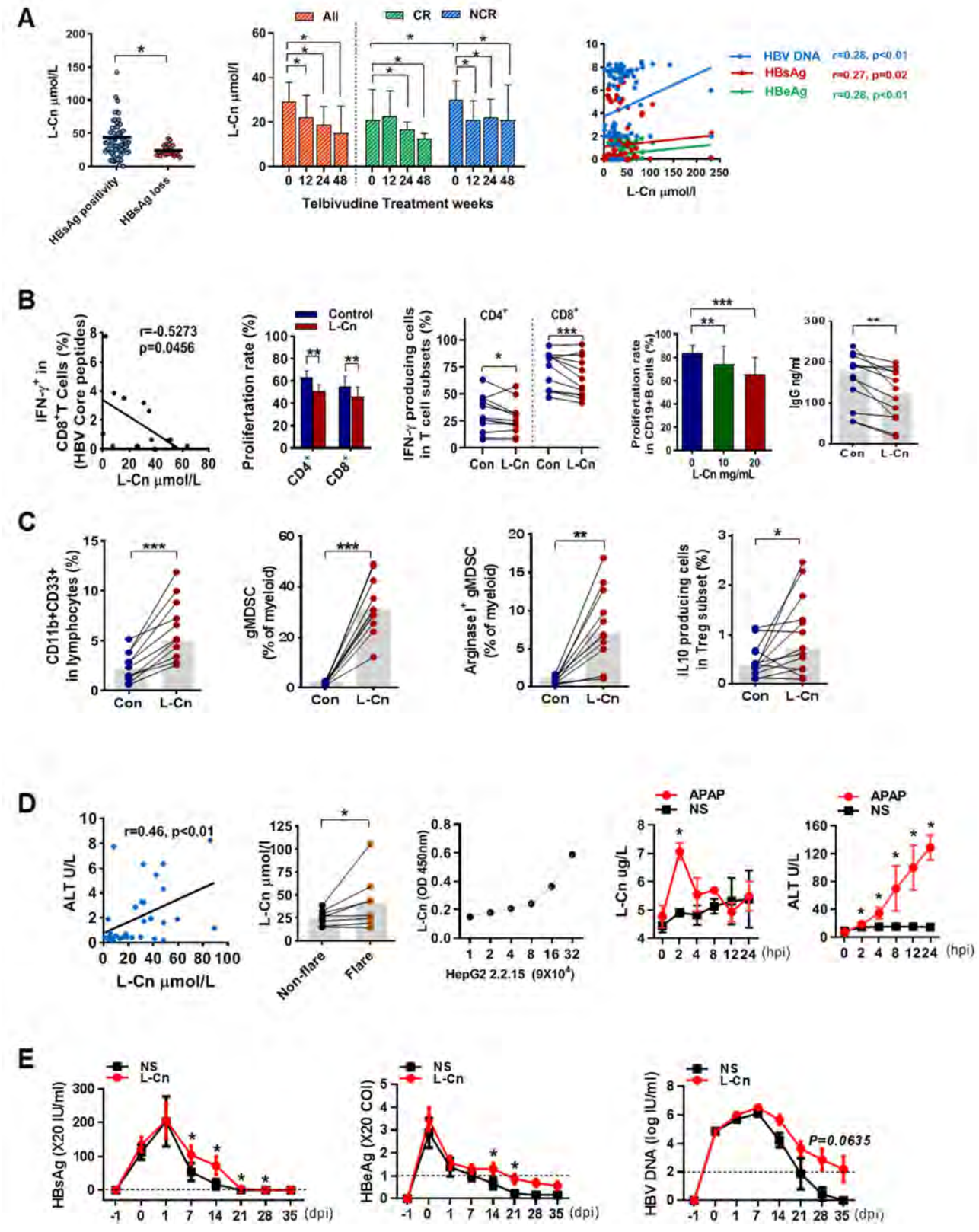


Figure: (abstract: FRI371)

loss in CHB patients has been documented. However, the underlying mechanisms are less well understood.
Method: Ninety-three patients with chronic HBV infection were defined as HBsAg positivity (≥100 IU/mL) or HBsAg loss (<0.05 IU/mL) group. HBeAg-positive CHB patients who participated in clinical trial with telbivudine treatment were classified into either a complete response (CR) group or a noncomplete response (NCR) group based on the status of HBeAg and HBV DNA at 48 weeks. Plasma levels of L-Cn were measured by ELISA. Flow cytometry and ELISPOT assay were performed to investigate the effect of L-Cn on lymphocytes. HepG2.2.15 cells were lysed and mouse model with acute liver injury was established by intraperitoneal injection of APAP to investigate the origin of L-Cn. In vivo effect of L-Cn was assessed by using an HBV mouse model with pAAV/HBV1.2 injection.
Results: Compared with patients with HBsAg loss, patients with HBsAg positivity had higher levels of L-Cn, and positive correlations between levels of L-Cn and the levels of HBsAg, HBeAg, and HBV DNA were observed. Interestingly, plasma levels of L-Cn were significantly decreased after telbivudine treatment, while the CR group showed lower levels of L-Cn than the NCR group at baseline (Figure A). Additionally, plasma levels of L-Cn were negatively correlated with the frequency of HBV-specific IFN-γ producing CD8+ T cells in patients with chronic HBV infection. In vitro assays revealed that L-Cn suppressed the proliferation and IFN-γ production of CD4+ and CD8+ T cells, and it also downregulated the proliferation and IgG production of B cells (Figure B). In contrast, L-Cn upregulated the frequencies of arginase-expressing gMDSC and IL-10-secreting regulatory T cells (Figure C). Additionally, plasma levels of L-Cn were positively correlated with ALT levels, and were significantly increased in patients with flare after the discontinuation of antiviral treatment. Moreover, lysates from HepG2.2.15 cells showed an ascending level of L-Cn in a cell-density-dependent manner. A transiently sharp increased levels of L-Cn accompanied by a gradually increased serum levels of ALT was observed in mouse model after the administration of APAP injection (Figure D). More strikingly, compared with HBV mice treated with normal saline (NS), HBV mice treated with L-Cn showed persistently elevated levels of serum HBsAg and HBeAg (Figure E).
Conclusion: L-Cn released from the injured hepatocytes displays immune suppressive properties and impedes HBsAg clearance, implicating that L-Cn may serve as a potentially therapeutic target for HBV infection.

FRI372
Interferon alpha-induced CXCL13 and IL-6 from intrahepatic monocytes facilitate HBV antigen seroconversion in chronic HBV infection
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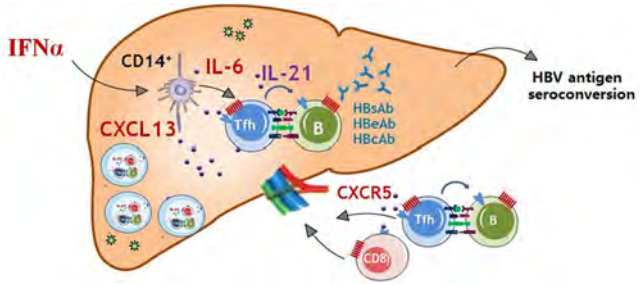
Background and Aims: It is well documented that interferon (IFN)α is superior to nucleos(t)ide analogs for the achievement of HBeAg/HBsAg seroconversion in chronic hepatitis B (CHB) patients, which indicates that IFNα could trigger effective humoral immunity in this setting; However, the underlying mechanism is not well understood.
Method: A total of 56 patients with chronic HBV infection were enrolled, including 24 patients with Peg-IFNα-2a treatment. Patients who achieved HBeAg seroconversion were defined as complete response (CR), the other patients were noncomplete response (NCR). The frequency of T cells, B cells, monocytes subsets and serum cytokines were detected. The effect of Peg-IFNα-2a on diverse immune cells were assessed. C57/BL6 WT mice were simultaneously administrated with pAAV-HBV1.2 and pIFNα plasmids by hydrodynamically injection of tail vein, levels of IL-6, CXCL13, HBsAb, and HBcAb were measured.
Results: A higher expression of IFNα-2a receptor was found in CD14+ monocytes and CD19+ B cells in treatment-naïve CHB patients. Although an increased frequency of plasmablasts was observed in patients with Peg-IFNα-2a treatment, in vitro assay revealed that Peg-IFNα-2a could not promote the proliferation and HBV-related antibodies production of B cell directly. Interestingly, Peg-IFNα-2a could promote the proliferation and cytokines production of monocytes, especially IL-6 and CXCL13. Notably, serum levels of IL-6 and CXCL13 were significantly higher in CR patients than that of NCR patients after Peg-IFNα-2a treatment. In vitro experiments showed that IL-6 triggered an enhanced production of IL-21 mainly from CXCR5 + CD4+ T cells, and IL-21 promoted the production of HBsAb and HBeAb from B cells. More importantly, an increased expression of intrahepatic CXCL13 and CXCR5+ cells were observed in the liver from HBV mouse model with exogenous IFNα injection, which can suppress HBV replication and promote the production of HBsAb.



Conclusion: IFNα-induced CXCL13 and IL-6 production from intrahepatic monocytes facilitate the recruitment of CXCR5+ cells and trigger IL-21 production from CXCR5 + CD4+ T cells, thus favoring potent B cell responses and HBV antigen seroconversion.

Viral hepatitis B/D: Clinical aspects except therapy

FRI373
Serum levels of circulating DNA species can predict the development of hepatocellular carcinoma in chronic hepatitis B patients under long-term oral antiviral therapy
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Background and Aims: Chronic hepatitis B (CHB) patients, even under effective long-term oral antiviral therapy, may develop hepatocellular carcinoma (HCC) which is the only factor that affects their liver-related mortality. Therefore, the accurate prediction of HCC

in CHB patients under therapy remains of great interest. The aim of this study was to investigate whether different species of circulating cell free DNA (cfDNA) may be used as markers to predict the development of HCC in treated CHB patients.
Method: Serum samples were obtained from 37 CHB patients who developed HCC during the first 5 years of oral antiviral therapy (HCC cases) and 74 CHB patients who did not develop HCC during at least 5 years of oral antiviral therapy (controls). HCC cases and controls were matched 1:2 for age, sex and platelets. cfDNA quantity was evaluated (before HCC diagnosis in HCC cases) by performing quantitative real-time polymerase chain reaction (PCR) of the housekeeping gene GAPDH. The levels (genomic equivalent [GE]) of the Alu repeats of 115 and of 247 bases, the levels of RNAse P coding DNA and the copies of mitochondrial DNA were also assessed by quantitative real-time PCR.
Results: Median [IQR] cfDNA concentration and levels of Alu115 were similar between HCC cases and controls (65 [112] vs 55 [137] ng/mL and 246 [482] vs 233 [567] GE, $p > 0.290$). In contrast, the levels of Alu247 were significantly higher in patients who developed HCC (349 [292] vs 69 [251] GE, $p = 0.042$). However, the Alu 247/115 ratio, used as an index of DNA integrity, did not differ significantly between the two groups (0.74 [0.76] vs 0.57 [0.65], $p = 0.118$), which also had similar numbers of mitochondrial DNA copies (54 [55] vs 63 [68], $p = 0.535$). The median levels of RNAse P coding DNA were significantly higher in patients who developed HCC (68 [108] vs 15 [30] GE, $p < 0.001$). ROC curve analysis showed that the levels RNAse P coding DNA offered good prediction of subsequent HCC development (c-statistic: 0.80).
Conclusion: Serum levels of longer fragments (Alu247) of cfDNA and particularly those of the RNAse P coding DNA could be potentially used as non-invasive biomarkers for the prediction of the HCC risk in treated CHB patients.

FRI374
Immunological and virological markers during pegylated interferon therapy in HDV chronic hepatitis: any predictor of response?
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Background and Aims: Although several new compounds are currently under investigation, therapy with pegylated interferon-alpha-2a (Peg-IFN) is still considered the standard of care for patients with HDV chronic hepatitis (CHD). This study investigates host and virological patterns during Peg-IFN treatment as feasible predictors of response.
Method: Eighty sequential serum samples from 16 CHD patients (HBV genotype D and HDV genotype 1) were tested. Serum HDV-RNA and HBV-DNA were detected by real-time quantitative PCR; HBsAg, HBcrAg and anti-HBc IgG levels were determined by chemiluminescence immunoassay (Lumipulse® G system, Fujirebio, Japan). Serum concentration of 12 soluble immune modulators (IL-1ra, IL2-ra, IL-6, IL-7, IL-10, IL-12p70, IL-13, IL-16, IP-10, INFgamma, TNFalfa e TNFbeta) were evaluated by LUMINEX-based multiplex technology. Virological and immunological markers were measured at baseline, 6, 12, 18 and 12 months after end of therapy (12MFU).
Results: Overall, 8 patients cleared HDV RNA during treatment and were still negative at 12MFU (responders, R), among them 2 cleared HBsAg and 1 became anti-HBs positive. Eight patients were not responders (NR). Except anti-HBc IgG,the other virological markers HDV-RNA, HBsAg and HBcrAg showed mean baseline levels significantly lower in R then in NR (Table). By combining baseline levels and reduction values at 6 months, HDV RNA, HBsAg and HBcrAg showed a high accuracy in distinguish R and NR (area under the curve [AUC] = 0.969, 0.958, 0.891, respectively). Compared to normal physiological levels, CHD patients had lower values of IL-7 and Il-13; conversely, IP-10 levels were distinctly higher (more than ten-fold). No difference was observed in basal cytokines levels between R and NR. In all patients, both R and NR, we observed an increase of IL-2 ($p = 0.017$), IL-6 ($p = 0.061$), IP-10 ($p = 0.078$), and a reduction of IL-1 ($p = 0.003$) and IL-16 ($p = 0.014$) from baseline to the end of therapy.

Baseline	R	NR	p
HDV-RNA (Log IU/mL)	4.01 ± 1.38	5.54 ± 0.77	0.016
HBsAg (Log IU/mL)	3.12 ± 0.98	4.13 ± 0.62	0.027
HBcrAg (Log U/mL)	2.9 ± 1.2	4.5 ± 1.1	0.017
Anti-HBc IgG (Log IU/mL)	2.48 ± 0.75	2.74 ± 0.50	0.435

Conclusion: Peg-IFN treatment induces in CHD patients specific cytokines response showing a modulation of the innate IFN system but not predictive of the response to therapy. Conversely, the combination of baseline and early on-treatment 6 months values of either HDV RNA, HBsAg, HBcrAg, may be useful to predict treatment efficacy.

FRI375
Comparison of the risk of hepatocellular carcinoma in nucleos(t)ide analogue-naive chronic hepatitis B patients treated with entecavir versus tenofovir : a systematic review and meta-analysis
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Background and Aims: Tenofovir (TDF) and entecavir (ETV) are nucleos(t)ide analogues (NAs) preferred as first-line treatments for chronic hepatitis B (CHB) patients. Recently, efficacy for reducing incidence of hepatocelluar carcinoma (HCC) has become a critical concern in treated patients due to the long-term use of these drugs. However, existing studies show conflicting results. This meta-analysis aims to assess the efficacy in reducing incidence of HCC comparing TDF monotherapy with ETV monotherapy among CHB patients by analyzing their long-term clinical outcomes with hazard ratios (HRs).
Method: Two investigators independently searched the Cochrane Library, MEDLINE, and Embase databases for randomized controlled trials and nonrandomized studies (NRSs) using the keywords “Hepatocellular carcinoma”, “Tenofovir”, and “Entecavir”, and additional references were obtained from the bibliographies of relevant articles published through october 2019. The quality of each study was assessed using the Newcastle-ottawa scale and the gading of recommendations assessment, development and ealuation criteria.
Results: Twelve NRSs enrolling 51,648 patients met the inclusion criteria, 9947 in TDF group and 41701 in ETV group. For meta analysis, the incidence of HCC seems significantly low among the TDF group than ETV group [HR (95% CI) of 0.67 (0.51, 0.87), P = 0.003]. However, using adjusted HRs or HRs of propensity score (PS) matched subcohort in each studies, a statistically significant difference disappeared [In adjusted HR analysis : HR (95% CI), from 0.64 (0.41, 0.98) P = 0.04 to 0.83 (0.66, 1.05) P = 0.12] [In PS matched subcohort analysis : HR (95% CI), from 0.64 (0.47, 0.92) P = 0.01 to 0.86 (0.64, 1.16) P = 0.29].
Conclusion: There was no statistical significant difference when using HR which reduce heterogeneity of the TDF and ETV groups. Each involved study has a different observation period, study enroll year, inclusion & exclusion criteria, and baseline characteristics of host/hepatic/viral risk factors between TDF and ETV treatment groups. And each cohort, derived from separate countries, reflects

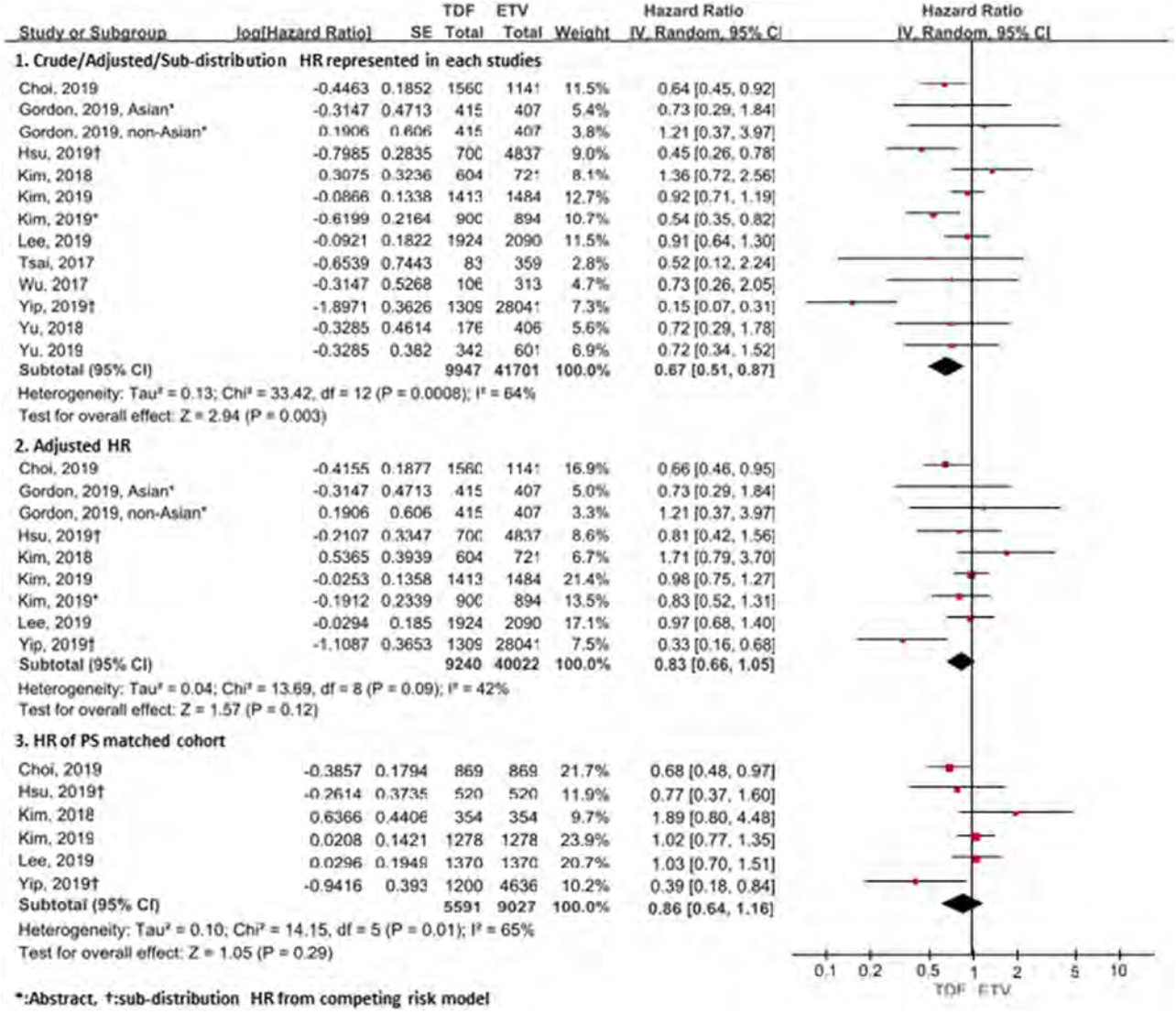

Figure: (abstract: FRI375)

different insurance, reimbursement policies, viral genotypes, and culture. We need further research comparing the efficacy of two drugs with standardized protocols reducing heterogeneity of treatment groups or large-scale randomized clinical trial to facilitate conclusive comparisons.

FRI376

Is it possible to stop nucleus(t)die analogue safely in patients with preemptive or preventive therapy for HBV reactivation?

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Background and Aims: Preventing or preemptive therapy with nucleos(t)ide analogue (NA) could prevent severe hepatitis related to HBV reactivation. However, it is not clear if NA can safely be stopped in such patients after cytotoxic therapies or during immunosuppressive therapies.

Method: A retrospective study, conducted in multiple hospitals, was used to evaluate 131 patients who initiated NA therapy between December 2007 and October 2018. In details, 103 patients were positive for HBV surface antigen (HBsAg) at baseline measured by (Architect HBsAg QT; Abbott Japan Corp., Tokyo). Preventive therapy with NA was started before cytotoxic or immunosuppressive therapy. Twenty-eight patients with resolved HBV infection were treated with NA after HBV reactivation during a monitoring period; preemptive therapy. The NA therapy could prevent severe hepatitis related to HBV reactivation in both groups. We examined anti-HBs and HB core related antigen (HBcrAg) examined by chemiluminescence enzyme immunoassay (Fuji-Rebio, Tokyo), using reserved serum of the enrolled patients. The relapse risk score was calculated by HBsAg and HBcrAg, according to the guideline of Japanese Society of Hepatology (JSH) HBV management.

Results: NA was stopped in 13 (13%) of 103 HBsAg positive patients, and in 15 (54%) of 28 HBV reactivated patients. We confirmed that clinical conditions including serological HBV markers at NA cessation were matched the criteria of JSH*. After NA cessation, HBV DNA was

redetected in 6 (46%) of 13 HBsAg-positive patients. However, ALT flare did not occur without NA treatment. We compared clinical characters between recurrence and non-recurrence patients in HBsAg positive group. High HBV DNA levels at baseline, and high amount of HBsAg both at baseline and at NA stop were marginal relationship to HBV recurrence. Relapse risk score '0' was significant association with non-recurrence ($p = 0.02$). In preemptive group, HBV DNA was redetected in 5 (33%) of 15 patients. HBV recurrence was observed in only anti-HBs negative patients at NA cessation. NA re-administration was initiated in 4 of 5 patients. Anti-HBs titers were increased over 10 mIU/mL in 2 of 4 patients after NA re-administration. *Hepatol Res 2014, 44 Suppl. 1

Conclusion: The HBsAg and HBcrAg scores predicted HBV recurrence after NA cessation in HBsAg-positive patients. In patients with resolved HBV, anti-HBs could be a predictive marker for NA cessation.

FRI378

Evolution of care quality metrics for chronic hepatitis B in the hepatitis C direct-acting antiviral era

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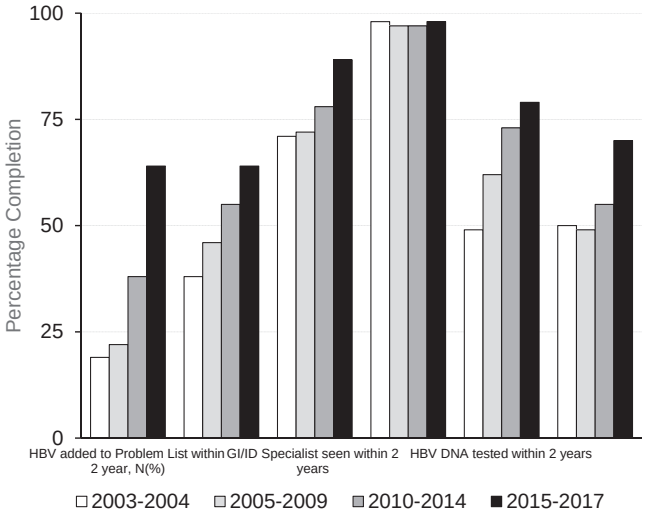
Background and Aims: National efforts to eradicate chronic hepatitis C (HCV) infection utilizing direct-acting antiviral (HCVDAA) were initiated in the Veterans Affairs medical system in 2014. Testing to identify patients at risk for associated hepatitis B reactivation (HBVr) soon became necessary. The objective of this study was to investigate whether the all-oral HCVDAA era was associated with increased recognition and delivery of guideline-recommended care for chronic hepatitis B (cHBV). We hypothesized that as a consequence of widespread HCVDAA treatment, referrals to specialist increased for HBV resulting in increased adherence to guideline-recommended care for HBV compared to the pre-HCVDAA era.

Method: Retrospective cohort study of veterans with at least one positive HBsAg (HBsAg+) result from January 1, 2003 to December 31st, 2017 using the VA Corporate Data Warehouse (CDW) were analyzed by era (2003–2004, 2005–2009, 2010–2014, 2015–2017). HCV coinfection was determined with positive HCV RNA PCR, and relevant covariates such as age, race/ethnicity, cirrhosis, and baseline laboratory testing were obtained through previously validated approaches. Process outcomes measured within 2 years of HBsAg+ result included: specialty care referral (GI/Hepatology/ID); Testing rates for ALT, HAVAb (IgG), HBV DNA, HBeAg, HBeAb, HCVAb (or HCVRNA), HDVAb (or HDVRNA), HIVAb (or HIVRNA; vaccination for HAV and HBV; any liver imaging and percentage time up-to-date with surveillance (PTUDS) in surveillance candidates; antiviral therapy in appropriate candidates (ALT $\geq 2 \times$ ULN, HBV DNA $\geq$ 2000 IU/ml).

Results: 16,673 individuals had a first HBsAg+ test result during the study period; of these, 9,521 could be confirmed as cHBV. There was a progressive decline in HCV coinfection rates (31% 2003–2004 to 15% in 2015–2017) but marked utilization of HCVDAA in candidates in later eras. Time-related increases in the following process measures were observed: outpatient visits with a GI or ID specialist within 2 years of HBsAg+ testing (71% to 89%), any type of liver imaging within 2 years of diagnosis (58% to 83%), HBV DNA testing (49% to 79%), HDV testing (26% to 35%), HBV DAA utilization in patients with active hepatitis and elevated HBV DNA titers (50% to 70%). By contrast, adherence with liver cancer surveillance remained static (40% ± 38% to 43% ± 35%). There were no significant interactions of process outcomes with HCV infection or HCVDAA exposure, but HCVDAA therapy was associated with improved survival in multivariable models. We however identify specific markers of high-quality HBV-directed care, specifically testing for concomitant HDV, that strongly associates with reduced mortality (HR 0.73 95% CI 0.66–0.81).



Conclusion: Quality of care for chronic HBV has significantly improved over time concomitant with efforts to eradicate HCV.

FRI379

Excess body weight is associated with HBV-related HCC despite antiviral treatment

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Background and Aims: Antiviral treatment cannot eliminate hepatocellular carcinoma (HCC) risk in patients infected with hepatitis B virus (HBV). It is unclear whether excess body weight contributes to HBV-related HCC development despite antiviral treatment.

Method: From January 2015 to December 2017, newly diagnosed HCC patients with hepatitis B surface antigen (HBsAg) positive were identified in Nanfang Hospital in Guangdong, Southern China. Excess body weight was defined as body mass index $\geq$23 kg/m^2. Antiviral history was defined as any prescription for anti-HBV medication >6 months prior to the date of HCC diagnosis, including interferon and nucleos(t)ide analogues. Multivariate logistic regressions were used to estimate adjusted association between excess body weight and HCC development despite antiviral treatment. We used HCC patients without antiviral history as a reference.

Results: A total of 2324 HCC patients with HBsAg positive were identified, 334 (14.4%) patients were defined as having antiviral history. Frequencies of excess body weight in patients with and without antiviral history were 57.8% and 42.9%, respectively ($p < 0.001$). Compared to HCC patients without antiviral history, HCC patients with antiviral history were more likely to have excess body weight (adjusted odds ratio [aOR] 1.48, 95% confidence interval [CI] 1.15–1.89). This phenomenon was only observed in patients with elevated alanine aminotransferase (ALT), but not in those with normal ALT, and in those with age $\geq$50 years, but not in those with age <50 years, and in smokers but not in never smokers (Table 1).

Table 1: Subgroup analyses for the association between excess body weight and HBV-related HCC despite antiviral treatment.

Subgroups	Unadjusted OR (95% CI)	P	Adjusted OR* (95% CI)	P
Elevated ALT (n = 1415)	2.54 (1.76–3.65)	<0.001	2.28 (1.52–3.42)	<0.001
Normal ALT (n = 909)	1.43 (1.04–1.97)	0.028	1.25 (0.86–1.83)	0.236
Age≥50 years (n = 1265)	2.25 (1.64–3.08)	<0.001	2.06 (1.42–3.02)	<0.001
Age<50 years (n = 1059)	1.37 (0.96–1.96)	0.082	1.21 (0.81–1.81)	0.341
Smoker (n = 879)	3.66 (2.26–5.91)	<0.001	3.16 (1.89–5.28)	<0.001
Never smoker (n = 1445)	1.38 (1.05–1.82)	0.020	1.23 (0.89–1.72)	0.201

*: Smoking history, live cirrhosis, hypertension, diabetes, high HBV DNA (≥2000 IU/ml), elevated ALT and tumor size were adjusted.

Conclusion: Excess body weight is involved in HBV-related HCC development despite antiviral treatment, especially in smokers.

FRI380

Commonly used non-invasive markers do not reliably predict liver fibrosis in those patients of chronic hepatitis B who really need it: a prospective multi-centre study

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Background and Aims: American Association for Study of Liver Diseases recommends liver biopsy in patients with Hepatitis B virus deoxy-ribonucleic acid (HBV DNA >2000 IU/ml) and alanine transaminase (ALT) levels between 1 and 2 X upper limit of normal (ULN), or age >40 years and normal ALT. European association of study of liver diseases recommends magnetic resonance elastography (MRE) or transient elastography (TE) for estimation of fibrosis. MR and TE are costly and not widely available, especially in resource limited settings. We did this study to assess performance of commonly used non-invasive markers in predicting liver fibrosis in patients with chronic hepatitis (CHB).
Method: Ethics committee approval was obtained. In a prospective multi-centric study in 3 university hospitals, from January 2016 to December 2018, 226 consecutive patients with asymptomatic CHB who did not fulfill the definitive criteria for therapy or no therapy as per AASLD guidelines underwent liver biopsy. Patients were classified in group A (Normal ALT and age >40 years, HBV DNA > 2000 IU/mL) and group B (ALT 1-2 X ULN, HBV DNA > 2000 IU/mL). The performance of simple non-invasive markers of fibrosis - Fibrosis 4 (FIB-4), Fibrofast 5 (FIB-5) and Aspartate transaminase platelet ratio index (APRI) to predict significant fibrosis [METAVIR stage > = 2] was evaluated. Significant inflammation was defined as Histology Activity Index > = 3.
Results: Out of the 226 patients (152 men, 40.0 ± 12.3 years), 107 (47.34%) had significant fibrosis and/or significant inflammation. Among group A, 15 (34%) patients had significant fibrosis and/or inflammation. In patients with group B, 26 (61.9%) HBeAg positive and 66 (47.14%) HBeAg negative patients had significant fibrosis and/or inflammation. Patients with ALT 1-2 X ULN were more likely to have significant inflammation than those with persistently normal ALT (60/81 Vs 21/81, p = 0.001).

Score	Cut off	Significant fibrosis (Mean ± SD)	Minimal/ no fibrosis (Mean ± SD)	AUROC	Sensitivity (%)	Specificity (%)
APRI	≥0.5	0.63 ± 0.44	0.46 ± 0.31	0.543	42	65.9
FIB-4	≥1.5	2.01 ± 0.92	1.88 ± 0.92	0.527	78.6	43
FIB-5	≤6.3	6.15 ± 0.35	6.29 ± 0.39	0.602	70	49.5

Conclusion: ALT of 1-2 X ULN is associated with significant inflammation. None of the non-invasive markers reliably predict liver fibrosis. Liver biopsy remains gold standard for detection of fibrosis and initiation of antiviral treatment with normal liver enzymes in resource limited settings where TE or MRE are not available.

FRI381

Evaluation of dried plasma spot on the cobas(r) plasma separation card as a sample type for hepatitis B virus load quantification on the cobas(r) 6800 system

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Background and Aims: Improving access to diagnostic testing in resource limited settings is critical to achieving hepatitis elimination goals and expanding coverage in these regions. Nucleic acid testing (NAT) is an accurate way to aid in the management of patients with hepatitis B virus (HBV) and enabling sample transportation over longer distances and harsher environmental conditions than EDTA plasma is necessary. Alternative sample types can facilitate the utilization of HBV diagnostic testing by permitting testing to be performed in remote areas or environments where phlebotomy may not be available. The **cobas®** Plasma Separation Card (PSC) is a device uses finger-prick blood to prepare dried plasma spots that are stable under high temperature and humidity conditions, allowing for sample transportation without the need of cold-chain but it was never evaluated as a sample type for HBV viral load monitoring.
The aim of this study was to evaluate the performance of the PSC as alternative sample type for HBV viral load quantification compared to plasma.
Method: We recovered whole EDTA venous blood from 67 clinical samples with positive HBsAg and HBV viral load determination. PSC samples were prepared by spotting 140 µL of whole EDTA venous blood and drying it at room temperature over a minimum of 4 hours. One spot of each PSC was eluted by incubating at 56 degrees C with Specimen Pre-Extraction Reagent for 10 minutes at 1000 rpm on a preheated thermo-shaker. Plasma EDTA direct samples and PSC eluted samples were analyzed by **cobas®** HBV Test in the **cobas®** 6800 system and paired results were compared.
Results: Correlation between PSC and plasma samples was linear (slope = – 1.24, intercept = 0.83, R^2 = 0.89) (Figure 1). For these samples, the mean viral load difference between plasma and PSC samples was – 1.81 log10 IU/mL (95% CI, – 2.22 to – 1.40). Detection for PSC above 1000 IU/mL occurred in all samples tested with PSC.

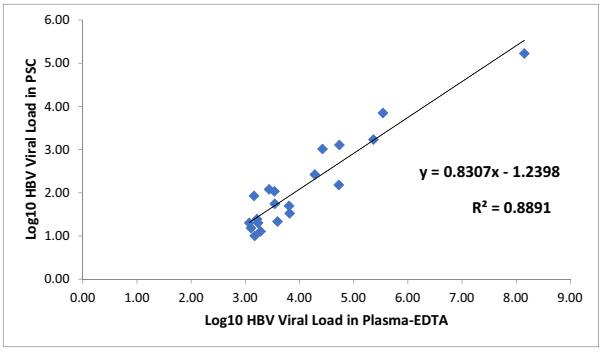

Figure: Comparison of results for PSC samples and Plasma-EDTA

Conclusion: Using PSC as an alternative sample type demonstrated a linear correlation to plasma viral load when tested with **cobas®** HBV Test, indicating that a correction factor could be applied to better align the PSC and plasma viral load. These results support the feasibility of PSC as an alternative sample type for detection and viral load monitoring of HBV.

FRI382

Genetic variants do not predict the development of hepatocellular carcinoma in cross-sectional and longitudinal studies including caucasian compensated HBV cirrhotics treated with NUC for 10 years

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Background and Aims: Signal transducers and activators of transcription (STAT4), Epidermal Growth Factor 1 (EGF1), Tolloid like 1 gene (TLL1), Myeloid-epithelial-reproductive tyrosine kinase (MERTK) and for domain II (MERTK2), Patatin-like phospholipase-3 gene (PNPLA3) and Membrane Bound O-Acyltransferase Domain Containing 7 (MBOAT7) genetic variants have been associated with the development of hepatocellular carcinoma (HCC) in Asian and Caucasian HBV patients. Here we assess if these variants predict the HCC onset also in HBV cirrhotics long-term treated by NUCs.
Method: TDF or ETV-treated Caucasian HBV-monoinfected compensated cirrhotics were consecutively enrolled in a longitudinal (n = 258) as well as in cross-sectional (n = 111) studies. At baseline longitudinal cohort were: age 61 (43–77) year, 82% males, 88% HBeAg negative, 60% NUCs-experienced, BMI 25 (17–40) kg/m^2, 12% diabetics, spleen length 11 (7–20) cm, 14% with esophageal varices, when transverse were: age 64 (51–77) year, 87% males, 93% HBeAg negative, 76% NUCs-experienced, BMI 25.1 (17–33) kg/m^2, 19% diabetics, spleen length 11 (7–20) cm, 24% with esophageal varices. Seven SNPs mapping on genes above cited (*rs7574865, rs4444903, rs17047200, rs4374383, rs6726639, rs738409* and *rs641738*) were analyzed by TaqMan genotyping assay.
Results: In the cross-sectional study, there were no significant difference between HCC patients (n = 51) and controls (n = 60) in rate of minor allele carriers of each SNPs investigated: 24% vs 27% for STAT4 (p = 0.63), 52% vs 74% for EGF (p = 0.09), 33% vs 30% for TLL1 (p = 0.75), 75% vs 77% for MERTK (p = 0.80), 57% vs 63% for MERTK2 (p = 0.53), 52% vs 40% for PNPLA3 (p = 0.33), 67% vs 62% for MBOAT7 (p = 0.72). In univariate only correlation with HCC was spleen length (11 vs 11.5 cm, p = 0.04). In the longitudinal cohort of 258 HBV patients followed on therapy for 123 (20–158) months, 45 (17%) patients developed an HCC after 56 (18–129) months. The 10-year cumulative HCC incidence was 20% (yearly rate 2.2%). The 10-year cumulative incidence of HCC was similar across different genetic variants while the only independent baseline predictors of HCC were and age (HR 1.09, 95%CI 1.0–1.1, p < 0.001) and spleen length (HR 1.33, 95%CI 1.1–1.5, p < 0.001).
Conclusion: In Caucasian HBV compensated cirrhotics treated with NUC, age and severity of portal hypertension, but not any of the 7 different genetic signatures, predicted the development of HCC in both longitudinal and cross-sectional studies.

FRI383

PAGE-B score is simpler and has similar predictive performance with the new Asian hepatocellular carcinoma risk scores in Caucasian chronic hepatitis B patients treated with long-term entecavir or tenofovir disoproxil fumarate therapy

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Background and Aims: Hepatocellular carcinoma (HCC) risk scores developed in untreated Asian chronic hepatitis B (CHB) patients offer poor/modest predictability in treated Caucasian patients, for whom HCC prediction is currently based on PAGE-B score. Recently, new HCC risk scores were developed in cohorts of treated Asian patients mainly based on age, gender and a parameter of liver disease severity. We assessed the predictability and comparative utility of the recent Asian HCC risk scores in treated adult Caucasian CHB patients, with or without well documented compensated cirrhosis.
Method: We included 1951 patients treated with entecavir/tenofovir (age 53 ± 14 years, males 71%, HBeAg-positive 18%, cirrhosis 28%, follow-up 7.1 ± 3.0 years). C-index was used to estimate the predictive performance of CAMD (age, sex, cirrhosis, diabetes), AASL (age, sex, cirrhosis, albumin), modified PAGE-B (mPAGE-B: age, sex, platelets, albumin) and PAGE-B score (age, sex, platelets) for HCC development within the first 5 years of therapy. The low-risk group cut-off of each score was used for estimation of sensitivity, specificity and negative predictive value (NPV) and the high-risk group cut-off for estimation of positive predictive value (PPV).
Results: HCC developed in 103/1951 (5.3%) patients during the first 5 years; 3- and 5-year cumulative HCC rates were 3.3% and 5.9%, respectively. All scores offered good 5-year HCC prediction (c-statistic - CAMD: 0.79, AASL: 0.81, mPAGE-B: 0.82, PAGE-B: 0.80). The proportion of patients classified into low-risk groups were 30% for CAMD, 22% for AASL, 24% for mPAGE-B and 21% for PAGE-B. Sensitivity and NPV were 100% for CAMD, AASL, PAGE-B and 98% and 99.5% for mPAGE-B, respectively. Specificity was 32% for CAMD, 25% for mPAGE-B and 23% for AASL and PAGE-B. The proportion of patients classified into high-risk groups were 24% for CAMD, 19% for AASL, 36% for mPAGE-B and 31% for PAGE-B, while PPV for 5-year HCC development was 13%, 18%, 13% and 13%, respectively.

Conclusion: In treated Caucasian CHB patients, with or without compensated cirrhosis, all recent HCC risk scores developed in Asian treated patients offer good 5-year HCC predictability, similar to that of PAGE-B score. PAGE-B and mPAGE-B scores are simpler in clinical practice, as they do not require an accurate diagnosis of cirrhosis, while the addition of albumin in mPAGE-B does not seem to offer an advantage in patients with well compensated liver disease.

FRI384

Hepatitis B core-related antigen and viral loads status impacts on the risk of hepatocellular carcinoma in patients with HBeAg-negative chronic hepatitis B virus infection

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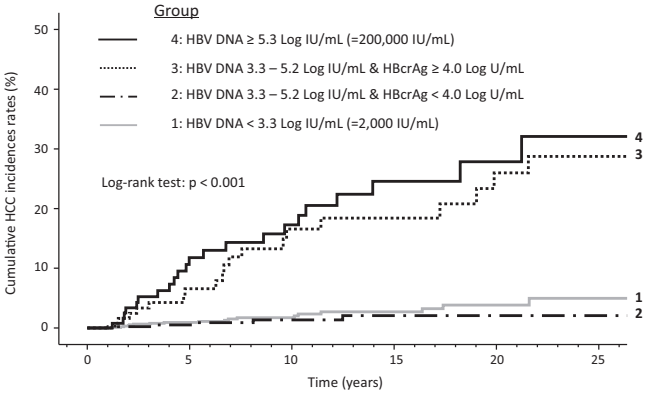
Background and Aims: Serum hepatitis B core-related antigen (HBcrAg) has been known as surrogate markers of intrahepatic covalently closed circular DNA (cccDNA). HBcrAg also reflects intrahepatic transcriptional activities of hepatitis B virus (HBV). Hepatocellular carcinoma (HCC) is likely to occur in patients with serum high viral loads. We examined whether HBcrAg and HBV DNA levels would have the impact on HCC development in chronically HBV-infected patients treated with or without nucleos(t)ide analogue (NA) treatment.
Method: We conducted a retrospective cohort study of in 1724 HBe antigen (HBeAg)-negative patients who experienced no antiviral treatment (untreated cohort), and 502 HBeAg-negative patients who received entecavir (ETV), tenofovir disoproxil fumarate (TDF), or tenofovir alafenamide (TAF) for more than one year in our institute as a first-line drug (NA-treated cohort) (452 patients started with ETV and 50 with TDF or TAF). Serum HBcrAg levels at baseline were measured using a commercial assay (Fujirebio Inc.). We categorized these cohorts into four groups stratified by baseline HBcrAg and viral loads as shown in figure. Patients were followed until any confirmed HCC diagnosis 1 year after the start of follow-up or NA treatment (primary outcome). We examined whether the stratification of baseline HBcrAg and viral loads would predict HCC development.
Results: During follow-ups of median 9.8 years, 69 patients (3.9%) had developed HCC (3.96/1,000 person-years) in untreated cohort. 1025 patients were categorized into group 1, 438 into group 2, 129 into group 3, and 132 into group 4 in untreated cohort. Cumulative HCC incidence rates were significantly higher in group 3 and 4 than those in group 1 and 2 in untreated cohort (Figure). This finding was observed in subgroup of patients with baseline low ALT. Multivariate Cox regression analysis showed that untreated patients in group 3 and 4 were likely to develop HCC than those in group 1 and 2 (hazard ratio (HR) of group 3: 5.20 and HR of group 4: 2.67). During follow-ups of median 7.0 years, 26 patients (5.2%) had developed HCC (7.44/1,000 person-years) in NA-treated cohort. HCC incidence rates were also significantly higher in group 3 and 4 than those in group 1 and 2 in NA-treated cohort as well as untreated cohort. Next, we compared HCC incidences in each group between untreated and NA-treated cohort. Multivariate Cox regression showed that NA-treated patients in group 3 and 4 were less likely to develop HCC than untreated patients in the same groups (HR of NA treatment in group 3: 0.26 and HR of that in group 4: 0.39), adjusted for baseline factors. However, this finding was not observed in patients with or without NA treatment in both group 1 and 2.



Conclusion: Patients with high HBcrAg and intermediate viral loads had the high risk of HCC as well as those with high viral loads. NA treatment greatly reduced HCC incidence in both group 3 and 4.

FRI385

Plasma adipocyte fatty acid-binding protein and adiponectin levels are associated with fibrosis regression in nucleoside analogue-treated chronic hepatitis B: a prospective study with paired transient elastography

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Background and Aims: Nucleoside analogue therapy (NA) can lead to fibrosis regression in chronic hepatitis B (CHB). Nonetheless, emerging evidence is demonstrating the impact of metabolic parameters on the fibrogenic process in CHB. We aim to study the association between adipokine levels and fibrosis evolution in NA-treated CHB patients.
Method: NA-treated CHB patients were recruited for baseline and 3-year transient elastography. Fibrosis stages was defined based on EASL-ALEH guidelines. Fibrosis regression and progression were defined as decrease or increase of ≥1 fibrosis stages from baseline respectively. Steatosis was defined as controlled attenuation parameter (CAP) ≥248 dB/m. Plasma adipokines including adiponectin, adipocyte fatty acid-binding protein (AFABP) and fibroblast growth factor 21 (FGF21) were measured by enzyme linked immunosorbent assay at baseline (Antibody and Immunoassay Services, The University of Hong Kong).
Results: 404 patients were recruited (72% male; median age 58.6 years; median NA treatment duration 74.5 months). 92.3% and 93.9% of patients had undetectable HBV DNA (≤20 IU/mL) at baseline and reassessment. Median adiponectin, AFABP and FGF21 levels were 10.4 (6.7–17.1) μg/ml, 96.5 (28.4–172.3) pg/ml and 12.6 (7.2–37.0) pg/ml respectively. Patients with steatosis, when compared with non-steatotic patients, had higher AFABP (117.0 vs 85.4 pg/ml), higher FGF21 (15.4 vs 10.2 pg/ml) and lower adiponectin (8.6 vs 13.3 μg/ml) (all $p < 0.05$). Patients with advanced fibrosis/cirrhosis had lower FGF21 (11.3 vs 13.6 pg/ml, $p = 0.045$) and higher AFABP (123.1 vs 69.1 μg/ml, $p < 0.001$) when compared with non-fibrotic patients. 17.8% of patients had fibrosis progression, while 21.8% of patients had fibrosis regression. Baseline FGF21, body mass index and metabolic syndrome were not predictive of fibrosis evolution. Among patients with advanced fibrosis/cirrhosis at baseline, lower levels of AFABP were independently associated with fibrosis regression (odds 1.005, 95% CI 1.001–1.010). Change in liver stiffness over 3 years correlated

moderately with AFABP (r = 0.308, p < 0.001). In the diabetic subgroup, adiponectin was an independent predictor of fibrosis regression (odds 1.296, 95% CI, 1.108–1.516, p = 0.001).
Conclusion: Adipokines including AFABP and adiponectin have prognostic value as biomarkers of fibrosis evolution during the treatment course of CHB, further illustrating the influence of metabolic factors in CHB-related treatment outcomes.

FRI386

Higher pregnancy hbcrag and pg HBV RNA concentrations are observed in treated and untreated chronic hepatitis B mothers with post-partum alt flares

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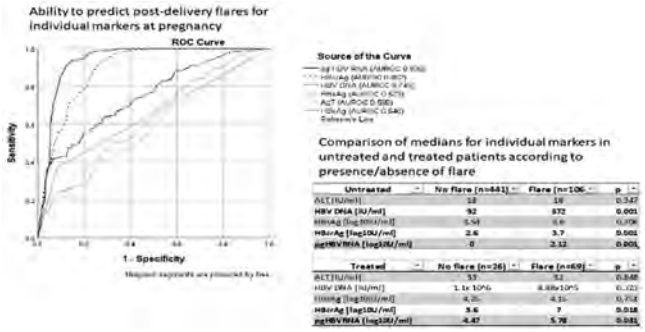
Background and Aims: Post-partum ALT increases are observed in 30% of HBsAg-positive mothers and can also be noticed in mothers administered nucleoside analogues (NA) to prevent mother-to-child transmission (MTCT). As such flares may be injurious we have studied the utility of novel and sensitive markers of cccDNA transcriptional activity i.e. hepatitis B core-related antigen (HBcrAg) and pre-genomic (pg) HBV RNA to predict post-partum ALT flares in both NA treated and untreated HBsAg-positive mothers. We aimed to evaluate the role of serum levels of HBcrAg and pgRNA in pregnancy to predict post-delivery ALT flares, their severity and by inference, a preference to continue NA therapy.
Method: Plasma samples from 642 HBsAg-positive pregnant women (pangenotypic cohort) were collected during the 2nd & 3rd trimesters and at 6, 12, 18, 24, 36 and 48 weeks post-partum. 103 (16%) were HBeAg-positive; median age 31 years. Samples were tested for HBeAg, HBV DNA (TaqMan, Roche; IU/ml); quantitative HBsAg (Abbott Architect; log_{10}IU/ml), HBcrAg levels (CLEIA Fujirebio; log_{10}U/ml) and pgRNA concentrations (real-time PCR assay Abbott Diagnostic; log_{10}U/ml). 95/642 mothers with HBV DNA concentrations >200,000 IU/ml started tenofovir prophylaxis from 28 weeks of gestation to prevent HBV MTCT. The ALT flares incidence and severe flares (defined as >10 × ULN) was correlated with HBcrAg and pgRNA in treated and untreated mothers.
Results: *Untreated cohort:* 106/547 (19%) of untreated mothers developed a post-delivery flare, but none was severe. Higher pre-delivery HBV DNA, HBcrAg and pgRNA concentrations were observed in untreated mothers with post-partum ALT flares than in mothers without a flare. ALT and HBsAg concentrations were similar in flare vs. no flare patients (Figure). *NA treated cohort: S*imilarly, higher pre-delivery HBcrAg and pgRNA concentrations were observed in NA treated mothers with a post-partum flare. 80/95 treated mothers stopped NA therapy post-partum (median 4 weeks). However no difference in the incidence of flares was observed in mothers discontinuing treatment versus in mothers who continued NA: 56/80 (70%) vs 13/15 (87%). Seven HBeAg-negative treated patients who stopped NA developed a severe ALT flare within 12 weeks post-delivery. High pre-delivery levels of HBcrAg (>7 log_{10}U/ml) and pgRNA (>4 log_{10}U/ml) were noted in mothers with severe flare. The flares resolved after re-starting NA. Thirteen (13%) mothers lost HBeAg and 6 (1%) lost HBsAg spontaneously within 1 year post-delivery (all mild flares). No ALT flares were associated with hepatic synthetic dysfunction.



Conclusion: Post-partum ALT flares are more common in pregnant women with higher pregnancy HBcrAg and pg HBV RNA levels, in both NA treated and untreated mothers. However high pre-delivery levels could suggest that NA therapy should be continued post-partum to avoid severe and injurious ALT flares.

FRI387

Gender disparity in the association of interleukin-10 and interleukin-12 polymorphisms with the progression of hepatitis B virus infection in Caucasians

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Background and Aims: Interleukin-10 (IL-10) and interleukin-12 (IL-12) are pivotal immunoregulatory cytokines which can affect the immune response against hepatitis B virus (HBV) infection. Variations in the IL-10 and IL-12 genes might influence the level of cytokine production and subsequently the course of HBV infection. Therefore, we evaluated whether there is an association between four common polymorphisms (SNPs) in these genes with the disease progression.
Method: The study cohort included 614 Caucasian patients (mean age 56 ± 15 years, 59% male) with chronic hepatitis B (CHB) and 239 individuals with spontaneous HBV surface antigen (HBsAg) seroclearance (SC). In the CHB group, 50% of patients were inactive carriers and 84% were HBeAg negative. 89(15%) had liver cirrhosis and 41 (7%) hepatocellular carcinoma, respectively. Host genomic DNA extraction and genotyping of the IL-10 SNPs rs1800896 and rs3024490 and IL-12 SNPs rs4568408 and rs2243115 was done from peripheral blood samples.
Results: Differences in the genotype distribution of the IL-10 SNP rs1800896 were observed between females with CHB and SC (p = 0.042) and between female inactive carriers and patients with chronic hepatitis B (p = 0.028). In multivariate analysis, the AA genotype was significantly associated with a reduced likelihood of spontaneous SC (OR = 0.56, p = 0.037) and a reduced likelihood of the development of an inactive carrier state (OR = 0.39, p = 0.003) in females. In contrast, the AG/AA variants of IL-12 SNP rs4568408 were significantly more frequent in chronically infected male patients with liver cirrhosis than in patients without liver cirrhosis (46% vs. 28%, p = 0.004). In multivariate analysis, the AG/AA genotypes were independently associated with an increased risk to develop liver cirrhosis with an odds ratio of 2.84 (p = 0.001) in males.
Conclusion: We identified a gender-related association of the IL-10 SNP rs1800896 and IL-12 SNP rs4568408 with different stages of HBV infection and liver disease progression in Caucasians. We suggest that genetic variants in components modulating innate immunity and inflammatory processes might play a role in the sex-related variability in response to HBV.

FRI388

Association between quantitative hepatitis B virus core antibody levels and surface antigen in chronic low viraemic patients

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Background and Aims: Hepatitis B virus (HBV) core antibody (Anti-HBc) is a marker of HBV core antigen-specific immune activity. Several studies have revealed that baseline quantitative Anti-HBc (qAnti-HBc) could predict the response of antiviral therapy. We performed a cross-sectional study to determine whether the total serum level of qAnti-HBc (immunoglobulins M and G) is associated with hepatitis B surface antigen (HBsAg) in low viraemic chronic HBV infected patients.
Method: Biochemical and virologic data were collected from 1493 HBsAg positive patients with HBV DNA < 500 IU/L and quantified qAnti-HBc at RuiJin Hospital, between August 2018 and September 2019. The association between qAnti-HBc and serum virologic markers was systematically analyzed.
Results: The mean qAnti-HBc level was 2.71 ± 0.69 log10IU/mL, which was higher in HBeAg negative patients of 2.86 ± 0.71 log10IU/mL than in HBeAg positive patients of 2.41 ± 0.52 log10IU/mL (p < 0.001). The correlation of the qAnti-HBc level and HBsAg was slightly positive in both HBeAg positive patients (pearson r = 0.10, p < 0.05) and negative patients (pearson r = 0.13, p < 0.001). Multivariate regression analysis revealed that HBsAg was independent factor associated with qAnti-HBc (beta = 0.10, p < 0.0001). Additionally, a nonlinear relationship was observed between qAnti-HBc and HBsAg. The qAnti-HBc level increased significantly only when HBsAg level above 512.86 IU/mL (log HBsAg 2.71) (adjusted beta = 0.19, 95% CI 0.04 to 0.12, p < 0.0001).
Conclusion: In chronic HBV infected patients with low viraemic, serum qAnti-HBc level was closely related to HBsAg in a nonlinear pattern. These findings suggest that monitoring qAnti-HBc level could serve as a useful marker for measuring host immune response against HBV.

FRI389

Risk of hepatitis flare in inflammatory bowel disease patients with previous hepatitis B virus exposure - results from a territory-wide Hong Kong ibd registry study

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Background and Aims: Biologics, thiopurines and steroid are commonly used in inflammatory bowel disease (IBD) and may

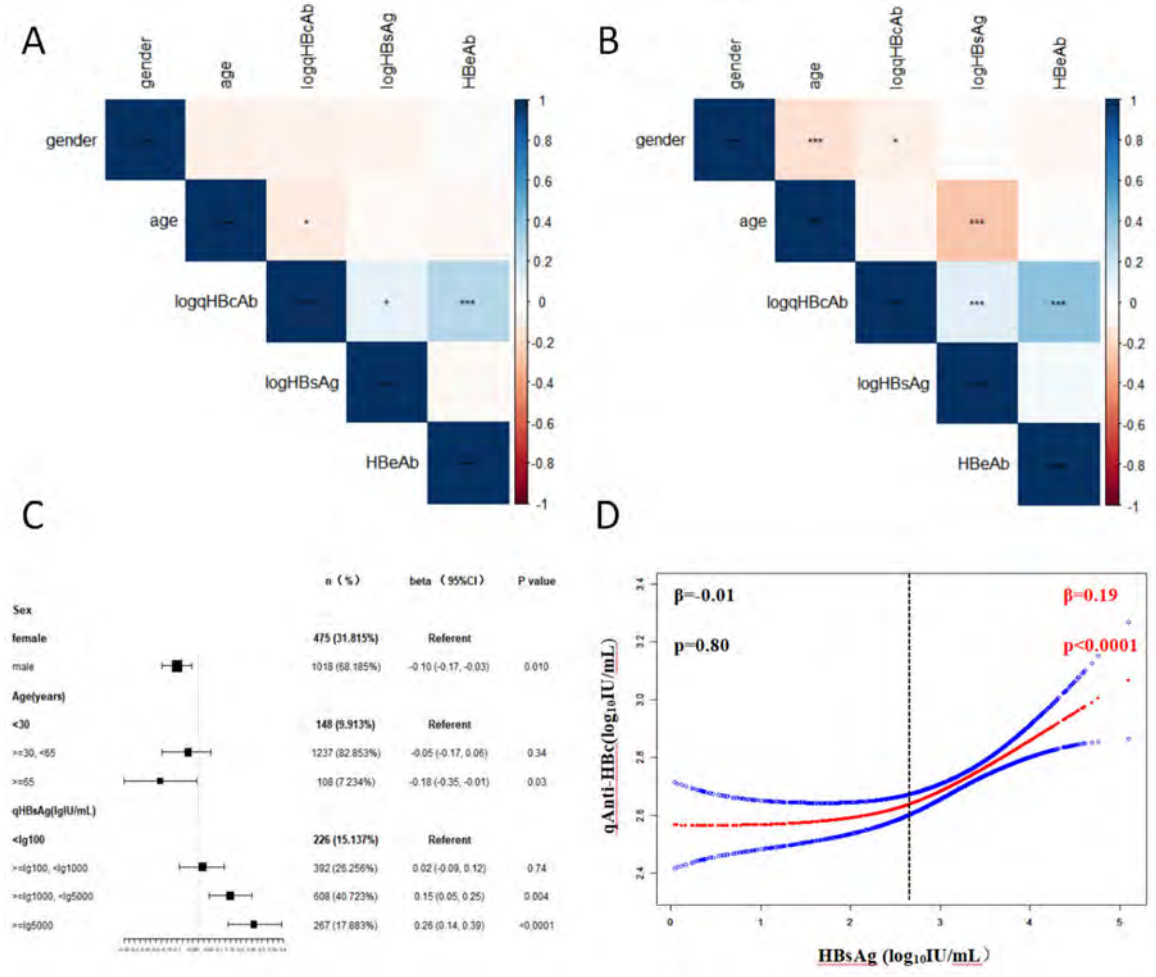


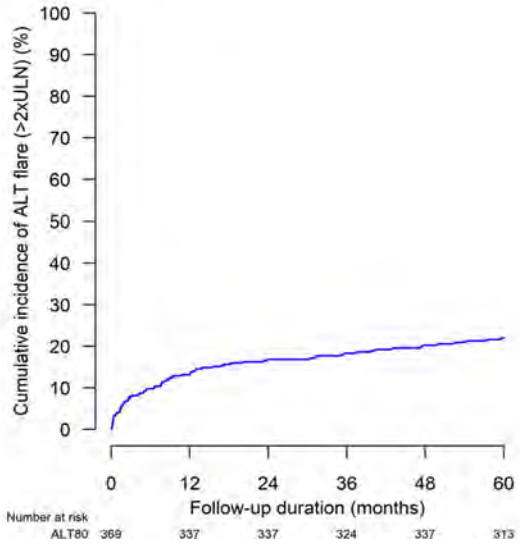
Figure: (abstract: FRI388) Heat map representation of correlation between qAnti-HBc and clinical parameters in HBeAg positive patients (A) and HBeAg negative patients (B). Forest plot for the multivariate analysis the association of clinical factors with qAnti-HBc adjusted for HBeAg status (C). Nonlinear pattern between qAnti-HBc and HBsAg adjusted for gender, age and HBeAg status (D).

cause hepatitis B virus (HBV) reactivation. Their exact risk of hepatitis B flare in patients with previous HBV exposure is poorly defined. We aim to study risk of hepatitis flare in IBD patients with previous HBV exposure.

Method: Patients were identified from territory-wide Hong Kong IBD Registry. IBD patients who were negative for HBsAg and received biologics or thiopurines or steroids from 1 January 2000 to 30 June 2019 were included. Patients who were positive for total antibody to hepatitis B core antigen (anti-HBc) and/or hepatitis B surface antigen (anti-HBs) were defined to have previous HBV exposure. Primary endpoint was development of hepatitis flare (alanine Aminotransferase [ALT) >80 U/L).

Results: Total 369 patients fulfilled inclusion criteria and were classified into 3 groups: anti-HBs positive only (n = 246); anti-HBs and anti-HBc positive (n = 78) and anti-HBc positive only (n = 45). Median follow up duration was 60 months (Interquartile range: 32.7–60 months). Seventy-six IBD patients (20.6%) developed hepatitis flare. Cumulative incidence of hepatitis flare were 13.2%, 18.3% and 22% at 12 months, 36 months and 60 months respectively. Use of thiopurine [adjusted hazard ratio (aHR) 2.56; 95% Confidence Interval (CI) 1.54–4.26, p < 0.001] and ever exposure to steroid [aHR 2.73; 95% CI 1.30–5.72; p = 0.008] were risk factors for hepatitis flare after adjustment of baseline ALT level. Use of biologics was not associated with risk of hepatitis flare [aHR 1.79; 95% CI 0.79–3.99; p = 0.14]. Ever exposure to steroid was associated with increased risk of hepatitis flare irrespective of peak dose (<20 mg prednisolone daily, 20–40 mg daily or >40 mg daily) [aHR: 2.34–4.18]. Fifteen patients (4.1%) developed severe icteric hepatitis flare (ALT >120 U/L and bilirubin >38 mmol/L). Cumulative incidence of severe icteric hepatitis flare were 2.7%, 7.2% and 8.4% at 12 months, 36 months and 60 months respectively.

Cumulative incidence of hepatitis B flare (ALT >80U/L) in inflammatory bowel disease patients with previous hepatitis B virus exposure



Univariate and multivariable analysis for hepatitis flare amongst IBD patients with previous HBV exposure

	Univariate analysis			Multivariable analysis		
Parameters	HR	95% CI	*P* value	Adjusted HR	95% CI	*P* value
Biologics	1.93	0.88–4.23	0.102	1.83	0.81–4.09	0.144
Aza	1.61	1.01–2.58	0.047	2.70	1.57–4.64	<0.001
Age	1.01	0.99–1.02	0.356	1.00	0.99–1.02	0.486
Male sex	1.13	0.71–1.80	0.601	0.94	0.58–1.52	0.805
IBD type CD/UC/IBD-U	1.06	0.67–1.67	0.797	1.29	0.77–2.16	0.328
Exposure to steroid	1.69	0.84–3.39	0.139	2.73	1.30–5.72	0.008
ALT	1.03	1.02–1.05	<0.001	1.03	1.02–1.05	<0.001

Conclusion: Amongst IBD patients with previous HBV exposure who were on biologics, thiopurines or steroid, 20.6% developed hepatitis flare. Use of thiopurine and ever exposure to steroid were risk factors for hepatitis flare. Use of biologic was not associated with risk of hepatitis flare.

FRI390

Sarcopenia is associated with type 2 diabetes and sedentary lifestyle in patients with chronic hepatitis B

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Background and Aims: Several evidences have shown that metabolic risk factors may play a role in sarcopenia. Of note, in cirrhotic patients, sarcopenia is common, and it is related to a poor prognosis. However, in chronic hepatis B (CHB) scenario, the relationship between sarcopenia, obesity, type 2 diabetes (T2D), hypertension and sedentary lifestyle has not yet been completely clarified. Thus, we aimed to evaluate the prevalence of sarcopenia and its association with metabolic risk factors in CHB.

Method: 121 patients [mean age, 48.5 ± 12.1 years; 56.5%, males; 80.2%, non-cirrhotic and 19.8%, with compensated cirrhosis; HBsAg/anti-HBe-positive, 91.7%; treatment-naïve, 57.0% and antiviral nucleos(t)ide analogues- (NUCs)- experienced, 43.0%] with CHB, prospectively, underwent scanning of the appendicular skeletal muscle mass (ASM), and fat mass by dual-energy X-ray absorptiometry. Muscle strength was assessed by dynamometry. Sarcopenia was defined by the presence of both low, ASM/height^2 (ASMI) and low muscle strength according to the European Working Group on Sarcopenia in Older People criteria. The cut-off points for low ASMI and low muscle strength, for women and men, were <5.45 and <7.26 kg/m^2 and <20 and <30 kg, respectively. The habitual physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) short version. The data were analyzed by logistic regression models. The study was approved by the Ethics Committee of the UFMG.

Results: Pre-sarcopenia (low muscle mass), sarcopenia and sarcopenic obesity (sarcopenia and body fat percentage >27% and >38% for men and women, respectively) were observed in 18.2% (22/121), 8.3% (10/121) and 5.0% (6/121) of the patients, respectively. In multivariate

analysis, adjusted by age, body mass index, glomerular filtration rate and sex, sarcopenia is positively associated with T2D (OR = 4.70; 95%CI = 1.02–21.72; p = 0.05) and low physical activity (OR = 3.08; 95%CI = 1.08–8.75; p = 0.04) and, inversely associated with NUCs therapy (OR = 0.23; 95%CI = 0.06–0.94; p = 0.04).
Conclusion: Sarcopenia is associated with metabolic risk factors in patients with CHB, specifically those with obesity, T2D and sedentarism. Antiviral therapy is associated with preserved ASM. These findings may influence clinical decision-making and contribute to the development of effective strategies to screen skeletal muscle abnormalities in CHB patients, independently of the stage of the liver disease.

FRI392

Incidence and predictors of hepatitis B surface antigen clearance among people living with HIV and hepatitis B

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Background and Aims: Incidence of hepatitis B surface antigen (HBsAg) clearance is reported to be 0.7% to 1.02% per year among those with hepatitis B virus (HBV). Low HBV DNA or HBsAg levels and hepatitis B e antigen (HBeAg) negative status was associated with HBsAg loss. However, incidence and predictors of HBsAg loss among people living with HIV (PLWH) is not known.
Method: We conducted a retrospective multi-center analysis of PLWH coinfected with HBV. Data were collected from 3 HIV clinics in Dallas, San Antonio, and Houston, Texas. Chronic HBV was defined by: (1) hepatitis B core IgM negative and HBsAg+, HBeAg+, or HBV DNA+ or (2) HBsAg+, HBV DNA+, or HBeAg+ two times 6 months apart. Incident HBSAg loss was defined as loss of HBsAg >6 months after initial HBV diagnosis. Hazard risk ratio for HBsAg clearance was examined by univariate and multivariate analysis.
Results: We examined 567 PLWH with chronic HBV (86% Male; 61% Black and 15% Hispanic; 41% uninsured, 44% with AIDS at baseline) who had 4,127 years of follow-up. HBsAg loss occurred in 10.6% and among those with HBsAg loss, 62% developed anti-HBs. The incidence of HBsAg loss was 1.45% per year and anti-HBs developed 0.88% per year. We examined race, HIV risk factor, HBeAg-status at baseline, HBV DNA suppression at baseline, HIV RNA suppression at baseline, cirrhosis, hepatitis C, age, gender, insurance, and alcohol use. In a multivariable analysis, Hispanics (HR 3.00, 95% CI: 1.12–8.05),those with AIDS at baseline (HR 2.11, 95% CI: 1.26–3.54), injection drug use (IDU) as HIV risk factor (HR 2.74, 95% CI: 1.13–6.67) were at more likely to experience HBsAg loss, whereas those who were HBeAg+ at baseline (HR 0.36, 95% CI: 0.19–0.66) were less likely (Figure 1). Compared to those who had an increase in CD4 >300 cells/μL from baseline to end of follow-up, those with a decrease in CD4 cells were less likely to lose HBsAg (HR 0.31, 95% CI: 0.14, 0.68).

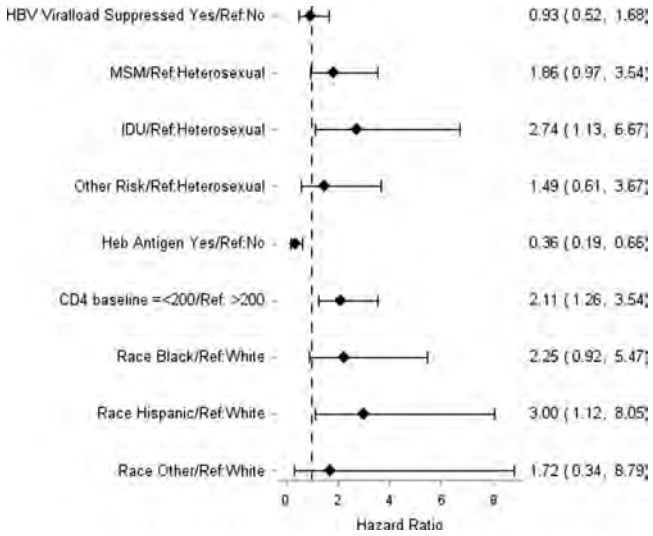

Figure 1: (abstract: FRI392)

Conclusion: HBsAg clearance occurs 70 to 200% times more frequently in PLWH compared to published incidence data in those with HBV alone. HBV surface antigen clearance in this cohort of PLWH is 3 times more likely in Hispanics than non-Hispanic Whites, and twice as likely in those with AIDS than those without. Those with HBeAg+ were 33% as likely to lose HBsAg compared to HBeAg-negative. Immune restoration may be a mechanism which increases likelihood of HBsAg clearance in HIV patients. Further studies are needed to understand why certain sub-groups have higher rates of HBsAg clearance.

FRI393

Rituximab monotherapy in anti-HBC positive patients with multiple sclerosis or neuromyelitis optica spectrum disorders is not associated with HBV reactivation

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Background and Aims: Immunosuppressant therapy in subjects with chronic hepatitis B virus infection (HBsAg) and resolved infection (antiHBc positive/HBsAg negative) may cause HBV reactivation. Anti-CD20 monoclonal antibodies are associated with greater risk of HBV reactivation, mainly in the context of hematological chemotherapy, although there are few data on the risk of monotherapy.
Method: All consecutive subjects with multiple sclerosis (MS) or neuromyelitis optica spectrum disorder (NMOSD) undergoing anti-CD20 monoclonal antibodies (rituximab, ocrelizumab) were included. Viral serologies were determined prior starting treatment. Those antiHBc+/HBsAg- not receiving other immunosuppressants, analytical follow-up was performed every 6 months (ALT, HBsAg, HBV-DNA, anti-HBs) without antiviral prophylaxis. HBV reactivation was defined by ≥2 log in HBV DNA or seroconversion to HBsAg+.

Results: 290 patients with MS or NMOSD underwent anti-CD20 agents: 260 (90%) rituximab and 30 (10%) ocrelizumab. Majority women (63%), Caucasian (97%), mean age 48 ± 10. All cases were HBsAg, anti-HCV and HIV negative. Anti-HBc antibodies were positive in 17 subjects (6%), and its prevalence was higher by 11% in subjects>50 years. Anti-HBc+ subjects were older (53.7 vs. 47.4, p = 0.015) and more frequently male (59% vs. 36%, p = 0.05) than anti-HBc-. Other immunomodulator drugs (59% interferon, 35% glatiramer acetate, 18% natalizumab), including corticosteroid bolus in disease relapses (a median of 10 bolus had previously received in 77% of anti-HBc positive). The median time between the diagnosis of neurological disease and starting anti-CD20 therapy was 18 years (0–37). All subjects presented undetectable HBV DNA at baseline, and median anti-HB titres were 35 mUI/mL (0–1000), being <10 mUI/mL in 5 (29%) of them. After a median follow-up of 12 months and 2 cycles of anti-CD20 (1–6 cycles), no cases of HBV reactivation or significant rise in anti-HBs levels were observed (p = 0.289). No subjects included in this study required corticosteroid bolus due to disease relapse, although 4 (23%) of them required dose adjustment due to toxicity or intercurrent infections.
Conclusion: Anti-CD20 monoclonal antibodies monotherapy in antiHBc positive subjects with multiple sclerosis or diseases of the spectrum of optic neuromyelitis does not seem to be associated with a higher risk of HBV reactivation, although longer follow-up is required to confirm these findings.

FRI394

Not uncommon: HBV genotype g co-infection in HBeAg-negative chronic HBV infected patients

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Background and Aims: A total of ten HBV genotypes (A-J) have been described. HBV genotype G (HBV/G) was mainly found in co-infections with other genotypes, predominantly with genotype A (HBV/A) and H (HBV/H). HBV/G is characterized by a 12 amino acid insertion in the core gene and two stop codons in the precore region that prevent HBeAg expression. We recently observed an impaired release of HBsAg and an accumulation of filamentous subviral particles in the ER and reduced activation of Nrf2 and cytoprotective genes in HBV/G expressing cells. In addition, *in vivo* reports suggest HBV/G as a risk factor for liver fibrosis in HBV/HIV co-infected patients. This study aimed to evaluate the prevalence and virologic characteristics of HBV/G in HBeAg-negative chronic infected patients.
Method: A total of 560 patients with HBeAg-negative chronic HBV infection were tested for HBV/G co-infection by a specific semi-nested PCR and direct sequencing of the core/precore and preS gene. Deep sequencing of HBV/G positive samples was performed to determine the percentage of HBV/G in the quasispecies. Co-infection was further correlated with clinical parameters and known basal core promotor (BCP) and precore (PC) mutations. Western blot analyses were performed using an SHBs-specific antibody.
Results: By direct sequencing, HBV/G was detected in 4% (7/161) and 8% (4/48) of patients infected with either HBV/A or HBV/E, respectively. Deep sequencing revealed that HBV/G was present as the major variant in the quasispecies of patients infected with HBV/A, while it was found only in low frequencies in patients co-infected with HBV/E. No significant impact of HBV/G co-infection on HBsAg or HBV-DNA levels was observed. In addition, co-infection with HBV/G was not associated with the presence of BCP (A1762T/G1764A) and PC (G1896A or G1896A/G1899A) mutations. Interestingly, the size of LHBs in serum samples from co-infected patients did not show the HBV/G-specific size difference in molecular weight.
Conclusion: A significant prevalence of HBV/G in co-infection with HBV/A and for the first time with HBV/E was detected in patients with HBeAg-negative chronic HBV infection. Interestingly, in HBV/A co-infected patients HBV/G represents the major variant in the quasispecies whereas in HBV/E co-infections HBV/G was found only as a minor variant. In contrast to recent in vitro data, HBV/G does not lead to a lower HBsAg level in the serum which might reflect HBsAg synthesis from integrated DNA in infected patients.

FRI395

Poor improvement of on-treatment FIB-4 index after initiation of nucleos(t)ide analogs is associated with development of hepatocellular carcinoma in both cirrhotic and non-cirrhotic chronic hepatitis B patients

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Background and Aims: Development of hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB) patients is not completely suppressed even under suppression of HBV replication by nucleos(t)ide analogs (NAs) treatment. While liver cirrhosis is known as the major risk factor for HCC, non-cirrhotic CHB patients often develop HCC. Although we previously reported HBV integration was responsible for HCC development during NAs therapy in such patients, clinically useful predictor for HCC development in non-cirrhotic patients is unclear. The aim of this study is to characterize the patients who develop HCC during NA treatment, and to clarify the risk factors for HCC especially in non-cirrhotic CHB patients.
Method: A total of 163 CHB patients who were treated with NAs were enrolled. Patients with previous history of HCC were excluded. All patients were followed up every 3 to 6 months, and pre- and on-treatment data were analyzed in patients with or without HCC development during follow-up.
Results: During median follow-up period of 6.8 years, the cumulative incidence of HCC at 10 years was 10.1%. In the univariate analysis of pre-treatment factors, cirrhosis (p = 0.020), lower platelet (PLT) counts (p = 0.028), and higher AFP levels (p = 0.043) were associated with HCC development. Of these, only cirrhosis was identified as the significant pre-treatment risk factor for HCC development by multivariate analysis (p = 0.021). Although levels of HBV DNA and serum inflammation markers such as ALT and AFP significantly improved after starting of NA therapy in most of the patients, changes of the fibrosis markers such as PLT, ALB, and FIB4 index were various among the patients. In the univariate analysis of on-treatment factors at 6 months and 12 months after the initiation of NAs, 6M-FIB4 index (p = 0.008), 12M-PLT (p = 0.047), 12M-ALB (p = 0.012), 12M-AFP (p = 0.022), and 12M-FIB-4 index (p = 0.010) were associated with HCC development. When changes in FIB-4 index during NAs therapy was

analyzed, 6M-/pre-FIB-4 ratio were significantly associated with HCC risk with a cutoff value of 1.0459 (p = 0.032), and the negative predictive values were extremely high at 0.980. In overall, 6M-/pre-FIB-4 ratio and cirrhosis were identified as the independent risk factors for HCC development by multivariate analysis. The cumulative incidence of HCC in 6M-/pre-FIB-4 ratio >1.0459 group was significantly higher in both non-cirrhotic and cirrhotic subgroups (p < 0.001).

Conclusion: Poor improvement of FIB-4 index even after initiation of NAs therapy predicts HCC development during NAs therapy both in non-cirrhotic and cirrhotic patients. Careful surveillance for HCC should be necessary in CHB patients without decrease in FIB-4 index during NAs treatment.

FRI396

The integrated use of accurate virological and serological HBV markers can help identifying HBsAg-negative/anti-HBC -positive patients at higher risk of HBV-reactivation and optimizing the duration of prophylaxis in oncohematological setting

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Background and Aims: Prevention of HBV-reactivation (HBV-R) in patients undergoing immunosuppressive therapy is still challenging. We investigate the role of HBV markers in predicting HBV-R in HBsAg-negative/anti-HBc-positive oncohematological patients.

Method: HBV-R rate is estimated in 107 HBsAg-negative/anti-HBc-positive patients (42 receiving rituximab [RTX], 40 hematopoietic stem cell transplantation [HSCT], 25 other chemotherapeutics [chemo]). All patients received lamivudine-prophylaxis for ≥18months after stopping immunosuppression (EASL guidelines) and were prospectively monitored every 3 months during and after prophylaxis completion. The role of HBV markers in predicting HBV-R is evaluated by testing 629 serum samples for highly-sensitive HBsAg (Fujirebio, HS-HBs; lower limit of quantification [LLOQ]: 5 vs 50 mIU/ml of routinely-used assays), HBV-DNA (Roche, LLOQ:20 IU/ml), quantitative anti-HBs and anti-HBc (Fujirebio, LLOQ:1.0COI). HBV-R is defined as serum HBV-DNA ≥ 20 IU/ml (Seto,2016).

Results: At baseline-screening, all patients have undetectable HBV-DNA and 67.3% is anti-HBs positive (median [IQR]:152[47–976]mIU/ml]. HBV-R occurs in 13/107 patients with the highest 5-year cumulative reactivation rate in HSCT (38% vs 21% for RTX and 10% for other chemo).

At HBV-R, median (IQR) HBV-DNA is 42(23–5831)IU/ml and ALT>ULN for 46%(median [IQR]:95[81–986]U/L). Among HBV-R cases, 5 develops HBV-R during and 8 after completing prophylaxis (median [min-max] months after prophylaxis completion:3[1–27]).

The analysis of serological markers during the entire monitoring reveals that an anti-HBc>3COI combined with anti-HBs persistently or declining to <50 mIU/ml correlates with a higher risk to develop HBV-R (46.2% of patients with anti-HBc>3COI+anti-HBs<50 mIU/ml vs 9.1% without this combination experiences HBV-R, P = 0.006, OR [95%CI]: 8.6[1.9–38.4]).

Furthermore, by monitoring virological markers, the positivity, confirmed in at least 2 time-points, to HS-HBs (detection failed by routinely used HBsAg-assays) and/or to HBV-DNA (detected below LLOQ) is another factor predicting HBV-R (45.5% of patients positive to HS-HBs and/or HBV-DNA vs 5.6% never positive to these markers experiences HBV-R, P < 0.001, OR [95%CI]: 14.2[3.2–62.9]).

Conclusion: HBV-R frequently occurs in anti-HBc-positive/HBsAg-negative oncohematological patients, particularly after completing antiviral prophylaxis. The combined usage of accurate HBV-markers can guide the identification of patients at higher HBV-R risk who need an extended prophylaxis.

FRI397

A comparative study of risks for hepatocellular carcinoma and mortality in chronic hepatitis B patients initially treated with entecavir or tenofovir

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Background and Aims: Risk evaluations of hepatocellular carcinoma (HCC) in entecavir (ETV) and tenofovir (TDF) treated chronic hepatitis B (CHB) patients have shown contradicting results in several retrospective cohort studies. Considerable “censored” data, insufficient “observation period”, and different “observation periods” between the drugs are unsolved issues in previous studies. We aimed to compare the incidence of HCC development between two oral nucelos(t)ide analogues over the same “observation period”.

Method: We examined retrospective data from treatment naïve CHB patients who were first treated with either ETV or TDF between 2011 and 2015 at nine academic hospitals in Korea. Clinical outcomes were observed for 4.7 ± 1.0 years and minimum observation duration was guaranteed for 3 years in both the groups.

Results: A total of 1,560 treatment naïve patients (753 in the ETV group and 807 in the TDF group) were included. In the entire cohort, mean and median “observation periods” were 4.6 ± 1.0 and 4.8 (Interquartile rage (IQR), 4.2–5.4) years, respectively. 92.4% of TDF and 92.7% of ETV treated patients were followed up during the observational period. In this cohort, 34 out of 753 patients (4.5%) in the ETV group and 45 out of 807 patients (5.6%) in the TDF group developed HCC under antiviral treatment during the follow up period; the incidences were not different between the groups. Moreover, these rates were not different between the drugs based on the 516-pair propensity score-matched population.

Conclusion: Incidence of HCC was similar between ETV and TDF treated patients over the same observation period (clinical trial No. KCT0003487).

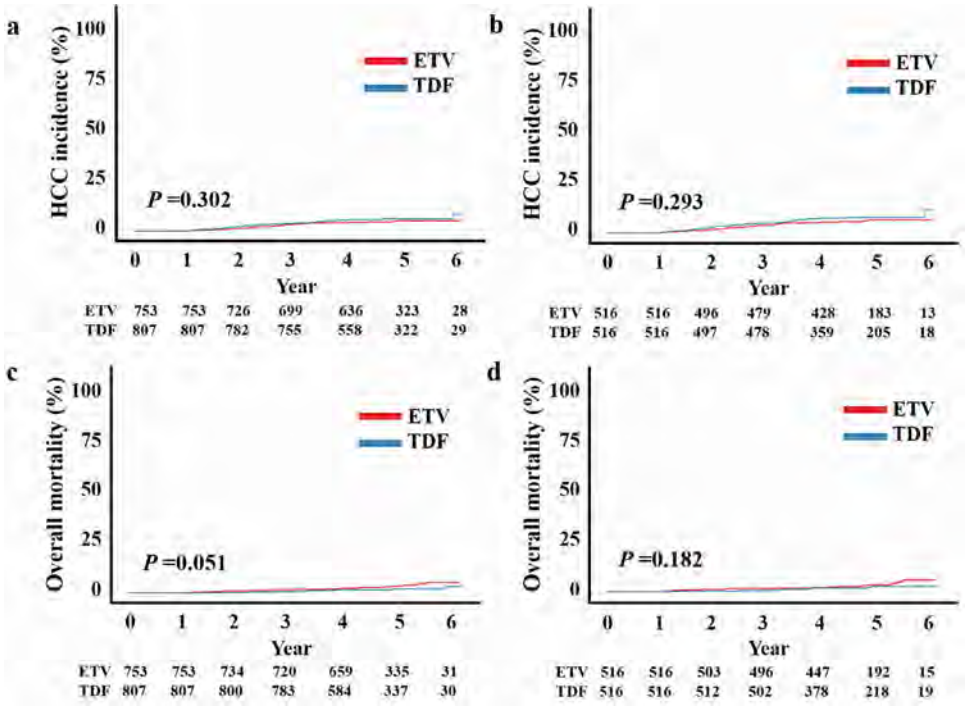

Figure: (abstract: FRI397)

FRI398

Reverse transcriptase droplet digital PCR versus reverse transcriptase quantitative real-time pcr for serum HBV RNA quantification

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Background and Aims: Serum hepatitis B virus (HBV) RNA is a novel marker reflecting the activity of intrahepatic covalently closed circular DNA (cccDNA). However, the optimal methodology for detecting HBV RNA has been a technical challenge and it is required to be applied in clinical setting.
Method: The performance of reverse transcription droplet digital PCR (RT-ddPCR) for quantifying HBV RNA was compared with that of reverse transcription quantitative real-time PCR (RT-qPCR) in serum samples collected from treatment-naïve patients with different phases of chronic hepatitis B (CHB). Serum HBV DNA and HBsAg quantifications were assessed by commercially available standard methods.
Results: A total of 417 serum samples, including 136 HBeAg-positive CHB and 281 HBeAg-negative CHB were examined. Serum HBV RNA levels measured by RT-ddPCR and RT-qPCR showed a high degree of linearity and quantitative correlation ($r = 0.929$, $P < 0.001$). The limit of detections of RT-ddPCR and RT-qPCR assays were approximately 10^2 and 10^3 copies/mL, respectively. Our results demonstrated that RT-ddPCR was superior to RT-qPCR in terms of its consistency for quantifying HBV RNA across all concentrations, particularly in the HBeAg-negative group with low HBV DNA levels. In the HBeAg-positive group, serum HBV RNA levels based on RT-ddPCR were moderately correlated with HBV DNA ($r = 0.591$, $P < 0.001$) and HBsAg ($r = 0.502$, $P < 0.001$). Among patients with HBeAg-negative CHB, serum HBV RNA levels were moderately correlated with HBV DNA ($r = 0.603$, $P < 0.001$) but had weak correlation with HBsAg ($r = 0.203$, $P = 0.001$).
Conclusion: The RT-ddPCR was more sensitive than RT-qPCR for measuring serum HBV RNA and could enhance the detection rate, particularly among the HBeAg-negative group with low viral loads. Thus, RT-ddPCR could serve as an optimal method for HBV RNA quantification in clinical practice.

FRI399

Early detection of chronic hepatitis B and risk factor assessment in Turkish migrants, Middle Limburg, Belgium

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Background and Aims: Turkey is an intermediate hepatitis B virus (HBV) endemic country. However, prevalence among Turkish migrants in Belgium is unknown, especially in those born in Belgium with a foreign-born parent, i.e. second-generation migrants (SGM). This study evaluated the prevalence of HBV infection and associated risk factors in Turkish first-generation migrants (FGM), i.e. foreign-born, and SGM.
Method: Between September 2017 and May 2019, free outreach testing for hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (anti-HBc) and antibodies against HBsAg was offered to Turkish migrants in Middle-Limburg, Belgium. Face-to-face questionnaire assessed HBV risk factors. HBsAg positive patients were referred and followed up. Turkish SGM were stratified into birth

cohort born before and after 1987, since those born after 1987 should be covered by the universal infant vaccination program.
Results: A total of 1,081/1,113 (97.1%) Turkish did go for HBV testing. Twenty-six (2.4%) were HBsAg positive; 11/26 were unaware of their status and 10/11 were successfully referred. HBsAg prevalence was 3.0% in FGM and 1.5% in SGM, $p = 0.070$. These numbers were 32.8% and 5.7% for anti-HBc, respectively, $p < 0.001$. Only one out of seven HBsAg positive SGM was born after 1987. Anti-HBc positivity in Turkish SGM born after 1987 was 1.1%, this was 9.1% for those born before 1987, $p < 0.001$.
Conclusion: Outreach testing was well-accepted and referral to specialist care was generally successful. National HBV screening should be implemented in the Turkish FGM population and might be considered in SGM not covered by primary prevention strategies.

FRI400
Three HBsAg kinetic profiles in HBeAg negative infection and chronic hepatitis are associated with different chances of HBsAg clearance

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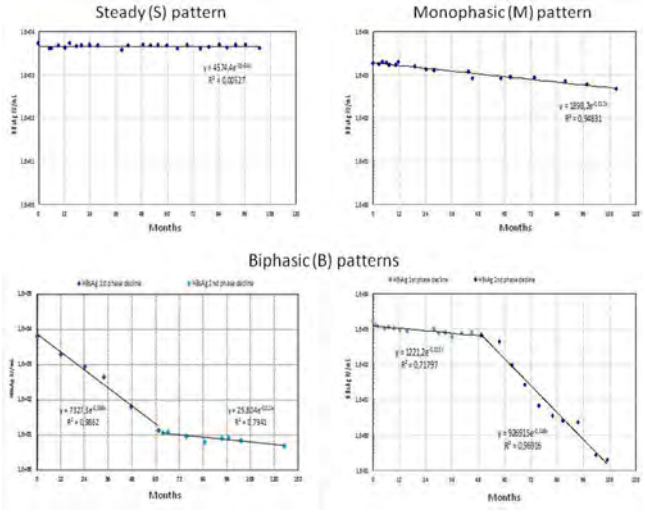
Background and Aims: Predictive markers of HBsAg clearance in HBeAg negative infection (ENI) and chronic hepatitis (CHB) treated with nucleos(t)ide analogues (NAs) remain an unmet need. We investigated whether the kinetic profile of HBsAg decline may predict this end point.
Method: HBV-DNA and HBsAg were measured at baseline (BL) and every 6 months thereafter in 89 ENI, 63 Low Viremic Carriers (LVC, HBV-DNA ≤ 20.000 IU/mL) and 90 CHB under NAs (55 with cirrhosis, CI). Individual HBsAg kinetics were plotted in semi-log scale and fitted with the exponential function y = a·exp^bx, with $-1 < b < 1$. Statistical analyses were performed by χ^2, Kruskal-Wallis, Spearman correlation test and logistic regression analysis.



Results: Median BL HBsAg (LogIU/mL) was lower in ENI vs LVC vs CHB [3.07 (−0.86/4.62) vs 3.36 (1.24–4.69) vs 3.52 (1.12/4.71); p = 0.003). The overall rate of HBsAg clearance was similar in ENI, LVC and CHB (9.0% vs 7.9% vs 6.7%, p = 0.846), however, median follow up was longer in CHB and LVC vs ENI [81.0 (11.6/204.6) vs 85.8 (33.1/226.7) vs 65.3 (25.2/155.9) mos., p = 0.004]. HBsAg < 100 UI/mL was reached within the end of follow up (EOF) in 63 (28.8%) of 219 cases with BL HBsAg>100 IU/mL: 15/72 (20.8%) ENI, 9/59 (15.3%) LVC and in 19/88 (21.6%) CHB (p = 0.608). Three HBsAg kinetic patterns were observed: Steady, S = 54 (22.4%); Monophasic, M = 146 (60.3%) and Biphasic, B = 42 (17.4%) decline (Figure). S was more frequent in ENI and LVC than in CHB (29.2% and 34.9% vs 6.7%); M was similarly distributed (57.3% vs 52.4% and 68.9%); B was more frequent in CHB than in ENI and LVC (24.4% vs 13.55% and 12.7%; p < 0.001). HBsAg clearance occurred in 9/146 (6.2%) with M and in 10/42 (23.8%) with B patterns (p < 0.001). In M the exponential decline was slower in LVC vs ENI vs CHB (median b = – 0.009 vs – 0.011 vs – 0.014; p = 0.016). In B, the 2nd phase exponential decline was faster in LVC vs ENI vs CHB (median b = – 0.108 vs – 0.087 vs – 0.040; p = 0.053). HBsAg clearance was independently associated with BL HBsAg Log IU/mL (OR = 0.521, 95%CI = 0.284–0.956, p = 0.035) and its Delta Log decline at 36 months (ΔLog36 m) (OR = 26.94, 95%CI = 4.386–165.481, p < 0.001). Overall, EOF HBsAg predicted by ΔLog36 m correlated with measured EOF HBsAg ($\rho = 0.897$), more strongly in ENI ($\rho = 0.964$) and CHB without CI ($\rho = 0.900$) than in LVC ($\rho = 0.883$) and CHB with CI ($\rho = 0.748$) and ΔLog36 m identified carriers who achieved EOF HBsAg<100 IU/mL with 78.7% Se, 99.4% Sp, 98.0% PPV, 93.0% NPV and 94.0% DA.
Conclusion: The lack of HBsAg decline was higher in untreated ENI and LV carriers (29.2% and 34.9%) than NAs treated CHB (6.7%). The monophasic exponential decline was predominant, and faster in CHB than in ENI and LV. HBsAg clearance occurred more frequently in biphasic (23.8%) than monophasic (6.2%) patterns, and was independently associated with BL HBsAg. The 36 months Delta Log decline identified carriers with EOF HBsAg<100 IU/mL with 98.0% PPV.

FRI401
Impact if HBV infection in HCV/HBV coinfected patients treated with DAAs in north Italy

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Background and Aims: Several small series have described the incidence of HBV reactivation during direct -acting antivirals (DAAS), so far. However, many key issues remain unresolved. Aims of the present study was to evaluate both the incidence and the clinical impact of HBV reactivation in a large cohort of HCVHBV co-infected-patients treated in North Italy.
Method: Between January 2015 and December 2018 data from a common web based program (NAVIGATORE), 16.161 patients treated with DAAs in Veneto and Lombardia were collected. After the first data extraction, centers were asked to provide further details on both the clinical course and outcome of HBV reactivation.
Results: Overall, the prevalence of HBV/HCV co-infection was 1.39% (226/16.161). HCV/HBV co-infection was more frequent in male ($p < 0.01$), and in HIV positive versus HIV negative patients (28.3% versus 12.7%, $p < 0.01$). HBV/HCV co-infected patients had more severe liver disease compared with HCV mono-infected (F3-F4 65.9% versus 57.1%, $p < 0.01$). HCV/HBV co-infected patients were comparable with HCV mono-infected in term of HCV baseline viral load, and SVR 12 (96.0% versus 96.6%). The incidence of HCC during follow-up was more frequent in HBV/HCV co-infected than in HCV mono-infected patients (2.2% versus 0.8%, $p < 0.05$). HBV-DNA was serially monitored during and after treatment with DAAS in 160 (70%) patients. HBV reactivation (increment of HBV-DNA > 2 log from baseline) was observed in 9 cases (5.6%). None of the patients in treatment with (Nucleoside/Nucleotide inhibitors) NUCs (as part of treatment of HIV infection or those treated prophylactically with tenofovir, entecavir or lamivudine) showed HBV reactivation during the follow-up period. Only one of the nine cases which reactivated HBV showed transient mild hepatitis (ALT > 2 normal value). In additional 2 cases HBV reactivation was observed after the withdrawal of NUCs at the end of DAAs treatment (lamivudine) and after 12 weeks from DAAs suspension (entecavir).
Conclusion: In a large series from Northern Italy HBV reactivation after DAAs in HCV/HBV co-infected patients appears to be lower than previously reported-Prophylaxis or therapy with NUCs can avoid reactivation. However, the timing of withdrawal of NUCs prophylaxis remains to be clarified. Moreover, HBV positive patients must be closely monitored for the increased residual risk of HCC, after HCV eradication.

FRI402
Quantitative HBeAg varies in the different phases of HBV infection, and can predict therapeutic outcome in the setting of immunosuppression driven HBV reactivation

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Background and Aims: Qualitative HBeAg is a marker of active HBV replication and HBeAg loss is an important clinical and therapeutic end-point. Here, we quantify HBeAg level in different phases of HBV infection, its correlation with virological/biochemical markers and its role in predicting virological response to anti-HBV therapy.
Method: This study includes 86 eAg+ patients (pts): 20 with acute infection (AI) (HBcIgM+, median [IQR] HBV-DNA:8.3[7.9–8.7]logIU/mL, ALT:1556[142–2027]U/L), 14 with eAg+ chronic infection (CI) (median[IQR] HBV-DNA:8.1[4.7–8.5]logIU/mL, ALT<40U/L), 23 with eAg+ chronic hepatitis (CH) (median[IQR] HBV-DNA:8[6.8–8.5]logIU/mL, ALT:85[62–179]U/L) and 29 pts with immunosuppression-driven HBV reactivation (HBV-R) (median[IQR] HBV-DNA:6.8[5.5–8]logIU/mL, ALT:143[40–528]U/L, pre-reactivation status HBcAb+/HBsAg-). 15/29 pts with HBV-R were monitored for >12months after starting TDF or ETV therapy (median[min-max] months of follow-up: 21[12–54]). Quantitative HBeAg (qHBeAg) is assessed by DiaSorin LIAISON assay. Association of qHBeAg at HBV-R with the achievement of HBeAg loss after starting anti-HBV therapy is assessed by Fisher exact test.
Results: qHBeAg is higher in pts with HBV-R and AI (median[IQR] 930 [206–1945] and 754[210–3379]PEIU/mL) and decreases in pts with CI and CH (median[IQR] 655[0.9–1773] and 412[17–1850]).
qHBeAg positively correlates with qHBsAg in all the subsets of pts (Rho = 0.61, P = 0.003 for HBV-R, Rho = 0.78, P < 0.001 for AI, Rho = 0.71, P = 0.023 for CI and Rho = 0.75, P < 0.001 for CH) and with HBV-DNA only in CH (Rho = 0.59, P = 0.005). Moreover, qHBeAg negatively correlates with ALT in AI and CH (Rho = –0.59, P = 0.035; Rho = –0.42, P = 0.044), reflecting a modulation in HBeAg production by immune response.
Focusing on 15 pts with HBV-R starting anti-HBV therapy for >12 months, ALT normalization is achieved in 93% of pts while virological suppression and HBeAg loss in 60% and 53.3%, respectively. The combination of qHBeAg > 2000 PEIU/mL + qHBsAg > 52000 IU/mL at HBV-R is the only factor predicting no HBeAg loss during anti-HBV therapy (HBeAg loss in 0% pts with qHBeAg > 2000 PEIU/mL + qHBsAg > 52000 IU/mL vs 72.7% pts without this combination, P = 0.01, result not significant considering qHBeAg and qHBsAg separately).
Conclusion: HBeAg levels differ during the natural history of HBV infection and according to the extent of immunological pressure. In the setting of HBV reactivation, HBeAg levels can be useful in predicting virological response to anti-HBV therapy under iatrogenic immunosuppression.

FRI403
Development of a highly sensitive multiplex platform assay to monitor low levels of HBV DNA and pgRNA in samples from patients with chronic hepatitis B

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Background and Aims: HBV DNA levels, a surrogate of virus replication, and pregenomic RNA (pgRNA), a surrogate of cccDNA levels, are the strongest predictors of treatment response and clinical relapse. Current assays, such as the COBAS (AmpliPre/Cobas Taqman HBV test v2), quantitate HBV DNA levels ≥20 IU/mL, but are insufficient to monitor loss of residual virus in HBV patients on NrtI therapy. No commercialized assays are approved to detect plasma HBV pgRNA levels. More sensitive assays are clearly needed to guide treatment discontinuation decisions.

Method: Viral nucleic acids were purified from patient serum or plasma with a QIA Amp MinElute Viral Vacuum Kit. HBV DNA + pgRNA were quantified by RT-(q)PCR with the dual pan-genotypic primer probes. Highly sensitive PCR (HBV DNA) and RT-PCR (HBV DNA + pgRNA) assays were developed and calibrated against the WHO international standard for HBV DNA. Both PCR and RT-PCR products were sequenced for genotyping and resistance monitoring purpose.
Results: HBV DNA and pgRNA assay sensitivity and linearity were evaluated using an HBV GT B plasmid, AcroMetrix HBV GT E panel, and clinical samples containing a wide range of HBV DNA concentrations. For qPCR and RT-qPCR assays, the linear range was 2–9 $\log_{10}$ copies/mL, using 0.1 mL of serum/plasma. For the HBV PCR (DNA) and RT-PCR (DNA + pgRNA) "target detection" (TD) assays, pan-genotypic primers were designed to the conserved region of HBx and Core proteins. These protein regions were amplified by PCR and RT-PCR, respectively, separated by ethidium bromide agarose gels, and analysed by population sequencing. HBV nucleic acid TD was confirmed with sequence analysis aligned with pre-treatment sample sequences. Results from this dual probe qPCR assay were 5 times more sensitive than the COBAS assay, with HBV DNA detected in 22 additional samples from a panel of 69 clinical samples from NrtI-suppressed patients scoring "Target Not Detected" using the COBAS assay. These highly sensitive PCR (DNA) and RT-PCR (DNA + pgRNA) assays detected a single copy of HBV genome plasmid and HBV DNA down to 2–5 IU/mL.
Conclusion: The multiplex HBV nucleic acid assay platform allows simultaneous quantification and detection of HBV DNA and pgRNA with improved sensitivity and accuracy. Constant undetectable levels of total HBV nucleic acid level may be used for monitoring loss of key viral biomarkers on treatment and guiding discontinuation decisions.

FRI404

Very low rates of receiving antiviral therapy among treatment eligible chronic hepatitis B virus infected patients

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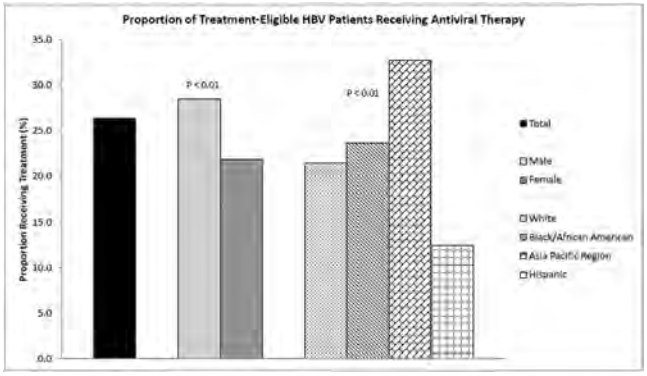
Background and Aims: Delays in initiation of antiviral therapy for chronic hepatitis B virus (CHB) patients contributes to continued disease progression to cirrhosis and development of hepatocellular carcinoma. CHB treatment rates are particularly sub-optimal among ethnic minority and immigrant populations, which are the highest risk groups for CHB. We aim to evaluate treatment eligibility and treatment rates among a large ethnically diverse multi-center adult CHB population.
Method: We retrospectively evaluated adults with CHB at four urban safety-net heath systems from January 1, 2010 to December 31, 2015, with a minimum 2-year follow-up. CHB was identified with ICD-9/10 diagnosis coding and confirmed with laboratory data. CHB treatment eligibility was determined using American Association for the Study of Liver Diseases criteria, which included assessment of hepatitis B virus (HBV) E antigen (HBeAg) status, serum alanine aminotransferase, HBV viral load, and fibrosis stage. Comparison of treatment eligibility and CHB treatment rates among eligible patients were performed using chi-square testing, and adjusted multivariate Cox proportional hazards models evaluated for predictors of receiving CHB treatment among eligible patients. Statistical significance was met with $p < 0.05$.
Results: Among 5,157 CHB patients (54.7% men, 35.7% white, 34.6% African American, 22.3% Asian, 7.7% Hispanic), 25.8% had cirrhosis,14.2% HIV co-infection, and 20.5% with HCV co-infection. Overall, 46.8% were eligible for CHB treatment, with significantly higher rates of treatment eligibility among men compared to women (58.2% vs. 32.9%, $p < 0.001$) and similar eligibility across race/ethnicity. Among treatment eligible patients, 26.4% received CHB treatment and only 10.0% received CHB treatment within 6 months of becoming eligible. Compared to men, women with treatment-eligible CHB were significantly less likely to receive therapy (21.8% vs. 28.5%; OR 0.72, 95% CI 0.58–0.91, $p < 0.01$) and Asians were significantly more likely to be treated compared to whites (32.7% vs. 21.4%; OR 1.51, 95% CI 1.12–2.04, $p < 0.01$).



Conclusion: Among a large, ethnically diverse multi-center cohort of CHB patients, only 26.4% of treatment eligible patients received CHB treatment. Women were the least likely to be treated, with nearly 80% of treatment-eligible not receiving therapy. Similarly, nearly 70% of treatment eligible Asians and 80% of treatment eligible whites and African Americans did not receive HBV treatment.

FRI405

Impact of hepatitis B virus-related immune reconstitution inflammatory syndrome on HBsAg loss in patients co-infected with human immunodeficiency virus

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Background and Aims: HBsAg loss, defined as functional cure, is an ideal therapeutic goal for chronic hepatitis B patients. In patients with HIV/HBV co-infection, liver-related mortality is higher than those with HIV or HBV mono-infection. It is thus strongly required to suppress HBV replication, or hopefully achieving HBsAg loss, to improve long-term prognosis in co-infected patients. After starting antiretroviral therapy (ART), HBV-related immune reconstitution syndrome (HBV-IRIS) occurs in some patients, which is clinically diagnosed as hepatic flare but without increase of HBV titers. However, it is yet to be determined the predictive markers of HBV-IRIS and its impact on the clinical course of HBV/HIV co-infection. We aimed to clarify these issues.
Method: We enrolled 56 HIV-infected subjects (median age, 41 years; $CD4^+$T cell count, 209 cells/μl). who had been HBsAg-positive for more than 6 months at the time of starting ART (HBeAg-positive/negative: 36/20). We observed patients for >3 years thereafter (median observational period, 9.1 years). Hepatic flare of HBV-IRIS was defined by an increase of ALT >5 × ULN, or ALT elevation of >200 IU/L from the baseline, which occurred within 12 months from the beginning of ART. We examined the correlation between clinical and viral markers and compared them between patients with and without HBV-IRIS.
Results: ourteen (25%) patients developed HBV-IRIS (average time to flare, 108 days; average ALT at flare, 592 IU/L). As predictors of HBV-

IRIS occurrence, younger age, increase of CD4 counts at one month after beginning ART (ΔCD4), and the regimens containing integrase inhibitors (INSTIs) were determined to be significant. Our new HBV-IRIS prediction model using age, ΔCD4 and INSTI (yes/no) distinguished HBV-IRIS patients from non-HBV-IRIS patients with an ROCAUC of 0.899, a sensitivity of 78.6%, and a specificity of 87.8%. The cumulative rate of HBeAg seroconversion in patients with HBV-IRIS was significantly higher than those in patients without HBV-IRIS (Log-rank, $p < 0.0001$, HR = 4.4). Furthermore, patients with HBV-IRIS subsequently achieved a significantly higher rate of HBsAg loss than those without HBV-IRIS (Log-rank, $p < 0.0001$, HR = 5.5). Uni-and multivariate analysis revealed that HBV-IRIS was the only contributing factor for HBsAg loss. All patients who showed >2 log reduction in HBsAg within one month after the onset of HBV-IRIS achieved HBsAg loss.

Conclusion: In HIV/HBV co-infected patients, age, an increase of CD4, and INSTI usage are predictors of HBV-IRIS occurrence. HBV-IRIS is associated with HBsAg loss, supporting the notion that immune reconstitution accompanying beneficial ALT flare is a key for attaining functional cure.

FRI406

Response to a double dose (40 mcg) and an accelerated schedule (0-1-2 months) of hepatitis B vaccine in patients with advance cirrhosis. A prospective study

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Background and Aims: The hepatitis B (HBV) vaccine is recommended in unvaccinated adults at high risk for HBV infection, including those with cirrhosis, to prevent HBV infection from triggering serious complications or death. However, the efficacy of HBV vaccine at a standard dose is low in patients with cirrhosis. Our aim was to evaluate the response to a double dose/accelerated schedule HBV vaccine in patients with decompensated cirrhosis.

Method: Prospective study including consecutive patients with liver cirrhosis admitted to the hepatology ward between March 2017 and April 2019. After assessing the immune status against HBV, all anti-HBs negative patients without exclusion criteria (HBsAg or antiHBc positive, age >75 years, hepatocellular carcinoma BCLC B-D, life expectancy <3 months) were offered HBV vaccination. The first dose of the HBVAXPRO 40mcg vaccine was administered during admission, and at month 1 and 2 in the Preventive Medicine Unit. After the first vaccination cycle patients with an anti-HBs <10 U/ml were offered a second vaccination schedule (40 mcg, 0-1-2 months).

Results: 496 patients were analysed; 91 (18.3%) were anti-HBs positive, and in 182 (45%) vaccination was not considered due to exclusion criteria. The vaccine was indicated to 207 patients. Ninety-nine (48%) completed the first cycle of vaccination, 28 died or were transplanted, 55 never attended and 25 did not complete the schedule due to their own decision or loss to follow-up. Thus, the acceptance rate was 56% (51% in alcohol consumers and 69% in the rest, $p < 0.05$). Of the 99 who completed the vaccine schedule, 63% were men, age 61 (54–67) years. The etiology of cirrhosis was alcohol (45%), hepatitis C (18%), NASH (14%) or autoimmune (8%). 72% were Child-Pugh (CP) B-C, 32% had diabetes, 33% were smokers and 23% alcohol consumers. By protocol, response (anti-HBs >10 U/ml) to the first cycle of vaccination was 22% and after the second schedule it increased to 61% (response to the second cycle 43%). 19% had a response greater than 100 IU/ml. The intention to treat response was 20.3% (42 out of 207 patients). No differences were found in the response according to the CP stage (68%, 62% and 50% for CP A, B and C respectively). The only predictor of non-response was autoimmune etiology (0% in the first cycle and 40% in the second cycle, per protocol).

Conclusion: This is the biggest prospective study evaluating HBV vaccination response in cirrhotic patients. More than 80% of patients with advanced cirrhosis admitted to a referral hepatology unit were unprotected against HBV. The response to a double dose and accelerated cycle of HBV vaccine was low (22%), but it improved significantly (61%) after a second cycle. Nevertheless, the low intention to treat response reinforces clinical guideline recommendation, which is HBV vaccination of patients with liver diseases before the development of cirrhosis.

FRI407

Presence of significant histopathology in HBeAg-positive chronic infection patients identified by four international guidelines: a Chinese multi-center study

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Background and Aims: HBeAg-positive chronic hepatitis B virus (HBV) infection, previously termed as "immune tolerant" phase, was defined with different threshold levels of HBV DNA and alanine aminotransferase (ALT) by international guidelines. In this study, we aimed to retrospectively analyze the performance of these guidelines in a Chinese multi-center cohort.

Method: From 2006 to 2018, a total of 1116 HBeAg-positive and treatment-naïve Chinese patients with liver biopsy samples were reviewed. We distinguished the HBeAg positive chronic infection patients from the others by ALT and HBV DNA threshold recommended by EASL (European Association for the Study of the Liver 2017), AASLD (American Association for the Study of Liver Diseases 2018), APASL (Asian-Pacific Association for the Study of the Liver 2015), and WHO (World Health Organization 2015). Among the patients with ALT ≤ 2 upper limit of normal (ALT ≤ 80 U/L, corresponding to EASL 2017), a liver biopsy with minimal or no liver necroinflammation or fibrosis ($G \leq 1$ and $S \leq 1$, Scheuer scoring system)was used as "gold standard" of a genuine HBeAg-positive chronic infection phase.

Results: The patients fulfilling each guideline criteria were grouped: EASL (ALT < 40 U/L and HBV DNA HBV DNA ≥ 107 IU/mL, n = 112), AASLD (ALT < 35 for men and 25 U/L for women and HBV DNA ≥ 106 IU/mL, n = 105), APASL (ALT < 40 U/L and HBV DNA ≥ 20000 IU/mL and age <30 y, n = 94), WHO (ALT <30 U/L for men and 19 U/L for women and HBV DNA ≥ 20000 IU/mL, n = 100). In applying the EASL, AASLD, APASL, and WHO criteria, the percentage of patients with significant histopathology ($G \geq 2$ or $S \geq 2$) was 35.7%, 30.5%, 45.7% and 42% respectively. The sensitivity and specificity values for HBeAg-positive chronic infection diagnosis were 75%, 67%, 15%, 62% and 95%, 94%, 96%, 94%, respectively. The EASL criteria (area under the receiver operating characteristic [AUROC] curve, 0.70; 95% confidence interval [CI], 0.65–0.74) performed better than AASLD criteria (AUROC, 0.66; 95% CI, 0.61–0.71), APASL criteria (AUROC, 0.64; 95% CI, 0.59–0.69) and WHO criteria (AUROC, 0.63; 95% CI, 0.58–0.68).

Conclusion: Though we couldn't deny the presence of significant histopathology in HBeAg-positive Chronic infection patients identified by the guidelines, ALT and HBV DNA threshold by EASL performed a better role in identifying HBeAg positive Chronic infection phase in Chinese Patients with Hepatitis B, compared with AASLD, APASL and WHO criteria.

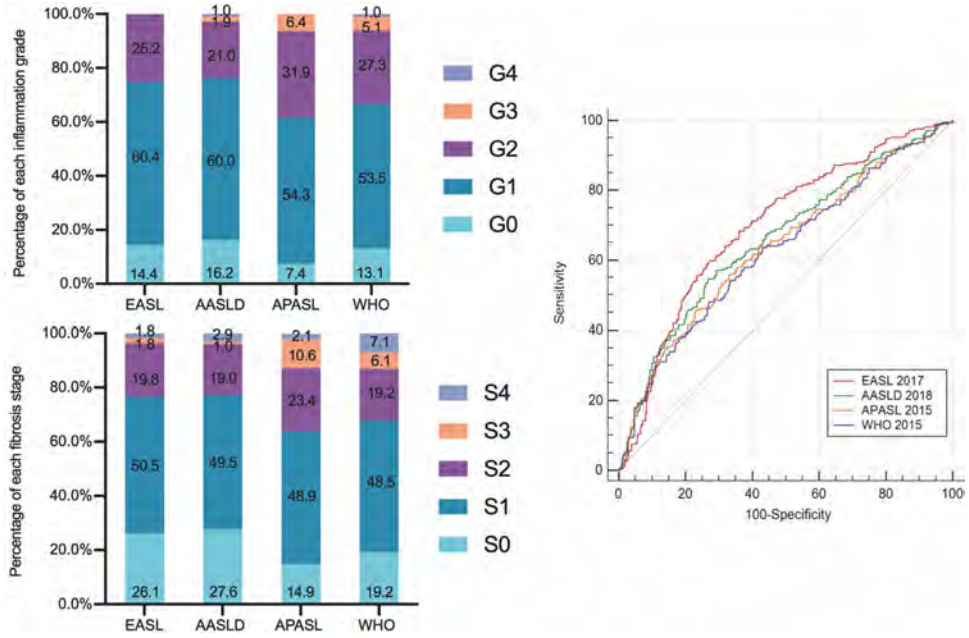

Figure: (abstract: FRI407)

FRI410

Evaluation of page-b and modified page-b scores to guide hepatocellular carcinoma surveillance in chronic hepatitis B patients on antiviral therapy - a territory-wide study of 32,150 subjects

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Background and Aims: PAGE-B and modified PAGE-B (mPAGE-B) scores are developed to predict risk of hepatocellular carcinoma (HCC) in patients on nucleos(t)ide analogue therapy. However, how and when to use these risk scores in clinical practice is uncertain.

Method: Consecutive adult patients with chronic hepatitis B who had received entecavir or tenofovir for at least 6 months between January 2005 and June 2018 were identified from a territory-wide database in Hong Kong. Performance of PAGE-B and mPAGE-B scores on HCC prediction at 5 years was assessed by area under the time-dependent receiver operating characteristic curve (AUROC), and different cut-off values of these two scores were evaluated by survival analysis adjusted for competing risk of death and liver transplantation.

Results: Of 32,150 identified chronic hepatitis B patients, 20,868 (64.9%) were male. Their mean age was 53.0 ± 13.2 years; 4,625 (14.4%) had cirrhosis. At a median (interquartile range) follow-up of 3.9 (1.8–5.0) years, 1,532 (4.8%) patients developed HCC. The AUROC (95% confidence interval [CI]) of PAGE-B and mPAGE-B scores to predict HCC at 5 years was 0.77 (0.76–0.78) and 0.80 (0.79–0.81), respectively ($p < 0.001$). Patients were classified as low, intermediate, and high HCC risk by the suggested cut-off values of PAGE-B and mPAGE-B scores (Figure). 9,417 (29.3%) patients were classified as low HCC risk by either PAGE-B or mPAGE-B scores; their 5-year

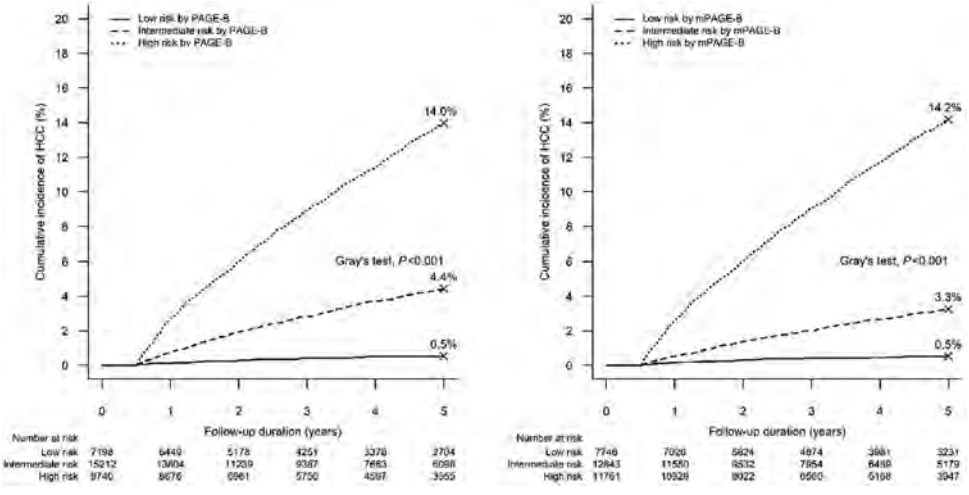

Figure: (abstract: FRI410)

cumulative incidence (95% CI) of HCC was 0.6% (0.4%–0.8%). This classification achieved a negative predictive value (NPV) (95% CI) of 99.5% (99.4%–99.7%) to exclude patients without HCC development in five years. The AUROC of PAGE-B and mPAGE-B scores at 2-year on-treatment to predict HCC was 0.78 (0.76–0.79) and 0.81 (0.79–0.82), respectively, which was comparable to that at baseline. Among 4,625 cirrhotic patients, 230 (5.0%) patients were classified as low HCC risk by either PAGE-B or mPAGE-B scores; their 5-year cumulative incidence (95% CI) of HCC was 5.6% (2.9%–9.5%). This classification achieved a NPV (95% CI) of 95.2% (91.4%–97.5%) to exclude patients without HCC development in five years.

Conclusion: PAGE-B and mPAGE-B scores can be applied to identify patients who have low risk of HCC development on antiviral therapy. These patients may be considered exemption from HCC surveillance due to their very low HCC risk. Caution should however be taken for patients who have liver cirrhosis.

FRI411

Clinical effectiveness of a newly developed and fully automated high-sensitive hepatitis B core-related antigen assay for monitoring nucleos(t)ide analogues therapy in hepatitis B envelope antigen-negative patients

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Background and Aims: Hepatitis B core-related antigen (HBcrAg) is one of important biomarkers that have an important role in chronic hepatitis B (CHB). A fully automated high-sensitive chemiluminescent enzyme immunoassay for detection of HBcrAg has been newly developing in Japan. Our aim is to demonstrate the clinical utility of the improved HBcrAg assay for monitoring the effect of nucleos(t)ide analogues (NA) therapy in hepatitis B envelope antigen (HBeAg)-negative patients.

Method: In this study, the performance of high-sensitive HBcrAg assay (HS-HBcrAg, Fujirebio, Inc.) was compared with that of conventional HBcrAg assay (Cv-HBcrAg, Fujirebio, Inc.) for monitoring NA treatment in HBeAg-negative patients. The sensitivity of HS-HBcrAg (2.1 Log IU/mL) is approximately 10-fold higher than that of Cv-HBcrAg assay (3 Log IU/mL). The total of 250 CHB patients treated with NA were enrolled, and 176 HBeAg-negative patients out of them were examined in our cohort. 1) In 93 NA-treated patients who have been undetectable for HBV-DNA, HS-HBcrAg was examined at the point before treatment and last visit. 2) In 40 naïve inactive carriers (IC), HS-HBcrAg was examined at first visit and last visit. The median durations of two groups were 14.8 [2.8–17.6] years and 7.3 [0.7–19.8] years, respectively. The study protocol was approved by the appropriate institutional ethics review committees.

Results: 1) In the sera from 93 patients undetectable for HBV-DNA, baseline HBcrAg was undetectable in the sera from 41.9% (39/93) patients by Cv-HBcrAg. Meanwhile, in the sera from 96.8% (90/93) patients, HBcrAg was detectable by HS-HBcrAg. The sera from 59.1% (55/93) patients showed HS-HBcrAg with ≥3 Log IU/mL, and 37.6% (35/93) patients had HS-HBcrAg with 2.1–3 Log IU/mL, which might be undetectable by Cv-HBcrAg. Note that the undetectable rates of HS-HBcrAg in NA-treated patients were only 1.1% at the point before NA-treatment and 4.3% at last visit. Meanwhile, those of Cv-HBcrAg were 16.1% at the point before NA-treatment and 41.9% at last visit (Table). 2) In naïve IC, undetectable rates of HS-HBcrAg were 15% at baseline and 25% at last visit. Meanwhile, those of Cv-HBcrAg were 65% at baseline and 82.5% at last visit (Table).

Conclusion: Compared with Cv-HBcrAg, HS-HBcrAg is much higher sensitive and could quantify HBcrAg for a long time regardless of NA-treatment. HS-HBcrAg assay would be more useful for the monitoring anti-HBV therapies in HBeAg-negative patients.

FRI412

Clinical efficacy of a newly developed high-sensitive hepatitis B core-related antigen assay for monitoring hepatitis B virus reactivation

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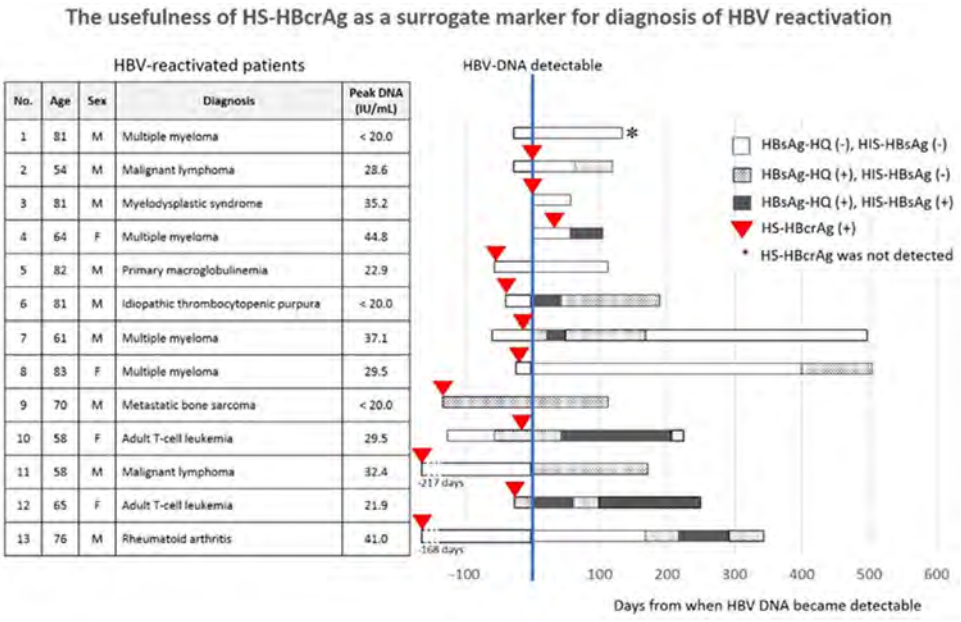
Background and Aims: Prevention and diagnosis of hepatitis B virus (HBV) reactivation is necessary for patients receiving systematic chemotherapy or immunosuppressive therapy. A fully automated high-sensitive chemiluminescent enzyme immunoassay for detection of HBcrAg has been newly developing in Japan. Our aim is to demonstrate the basic assessments of the new HBcrAg assay and present clinical utility of that for monitoring HBV reactivation to prevent the related hepatitis.

TABLE Undetectable rates of HBcrAg (%)

HBcrAg assay (Cut-off value, Log IU/mL)	Naïve IC (n=40)		NA-treated patients (n=93)	
	Baseline	Last visit	Baseline	Last visit
Cv-HBcrAg (< 3.0)	26 (65%)	33 (82.5%)	15 (16.1%)	39 (41.9%)
HS-HBcrAg (< 2.1)	6 (15%)	10 (25%)	1 (1.1%)	4 (4.3%)

Abbreviations: HBcrAg, hepatitis B core-related antigen; IC, inactive carriers; NA, nucleos(t)ide analogues; Cv-HBcrAg, conventional HBcrAg; HS-HBcrAg, high-sensitive HBcrAg.

Figure: (abstract: FRI411)



No.	Age	Sex	Diagnosis	Peak DNA (IU/mL)
1	81	M	Multiple myeloma	< 20.0
2	54	M	Malignant lymphoma	28.6
3	81	M	Myelodysplastic syndrome	35.2
4	64	F	Multiple myeloma	44.8
5	82	M	Primary macroglobulinemia	22.9
6	81	M	Idiopathic thrombocytopenic purpura	< 20.0
7	61	M	Multiple myeloma	37.1
8	83	F	Multiple myeloma	29.5
9	70	M	Metastatic bone sarcoma	< 20.0
10	58	F	Adult T-cell leukemia	29.5
11	58	M	Malignant lymphoma	32.4
12	65	F	Adult T-cell leukemia	21.9
13	76	M	Rheumatoid arthritis	41.0

Figure: (abstract: FRI412)

Method: A new high-sensitive HBcrAg assay (HS-HBcrAg, Fujirebio, Inc.) is more inexpensive than HBV-DNA test, and can measure HBcrAg within 30 minutes. The sensitivity of HS-HBcrAg (2.1 Log IU/mL) is approximately 10-fold higher than that of conventional HBcrAg assay (Cv-HBcrAg, Fujirebio, Inc.) (3 Log IU/mL). In this study, as fundamental examinations, specificity test for HS-HBcrAg, correlation analysis between HS-HBcrAg and Cv-HBcrAg, and linearity-of-dilution experiments of HS-HBcrAg were examined. After confirmation of the fundamental data, we enrolled 13 patients diagnosed as HBV reactivation during or after receiving systematic chemotherapy or immunosuppressive therapy. Their serial sera were examined by HS-HBcrAg, high-sensitive hepatitis B surface antigen (0.005 IU/mL, HBsAg-HQ, Fujirebio, Inc.) and conventional HBsAg (0.05 IU/mL) retrospectively to compare with the results of HBV-DNA (1.3 Log IU/mL). The study protocol was approved by the appropriate institutional ethics review committees.
Results: The specificity of HS-HBcrAg was 99.8% (494/495). Among 74 specimens positive for HBcrAg by both HS-HBcrAg and Cv-HBcrAg, correlation analysis between HS-HBcrAg and Cv-HBcrAg yielded the following values: $y = 1.00x + 0.10$, $r = 0.987$. Linearity-of-dilution experiments for HBcrAg-positive samples with high and low concentrations showed preferable results (% linearity for each: 99–101%). In our HBV-reactivated patients, the primary diseases were hematologic malignancies (10 patients), benign hematologic disease, autoimmune disease and solid cancer (1 patient each). Surprisingly, 9 of 13 patients with HBV reactivation showed earlier detection of HS-HBcrAg than HBV-DNA. Also, 9 HBV-reactivated patients showed earlier detection of HS-HBcrAg than HBsAg-HQ (Figure).
Conclusion: Fundamental and clinical examinations of HS-HBcrAg showed that HS-HBcrAg assay was reliable and useful as a surrogate marker for the monitoring HBV reactivation at early phase.

FRI413

Treatment advantage in HBV/HIV coinfection compared to HBV monoinfection in a South African cohort

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Background and Aims: Prompted by international targets for elimination of hepatitis B virus (HBV) infection, we performed a cross-sectional observational study of adults with chronic HBV (CHB) infection in Cape Town, South Africa. We characterised individuals with HBV monoinfection vs. those coinfected with HBV/HIV, to determine the effect of HIV coinfection, to evaluate the impact of current therapy and to shape improvements in clinical care as guidelines for antiviral therapy change over time.
Method: A cohort representing prevalent CHB was recruited at Tygerberg Hospital, Cape Town, South Africa, over one year (commencing July 2018). In this setting, antiviral therapy for HIV and HBV includes tenofovir disoproxil fumarate (TDF) as a first line agent. We recorded cross-sectional demographic, clinical and laboratory data. Ethical approval was provided by University of Oxford Tropical Research Ethics Committee and Stellenbosch University Human Research Ethics Committee.
Results: We prospectively recruited 112 adults with CHB; 55% were male, and 34% had HIV coinfection. Adults with HBV monoinfection were comparable to those with HBV/HIV coinfection in terms of age,

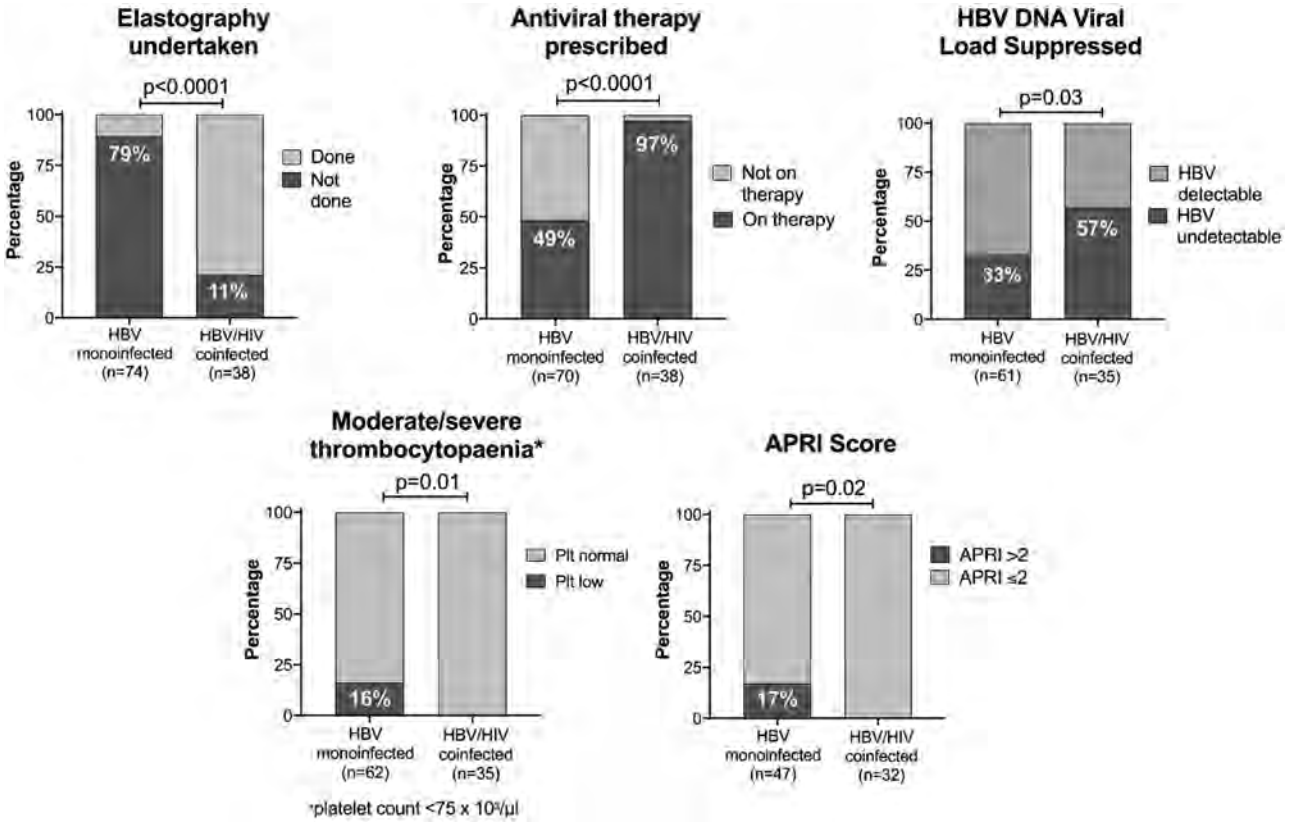

Fig 1: (abstract: FRI413): Comparison between HBV monoinfected and HBV/HIV coinfected adults.

sex, body mass and duration of antiviral therapy (p > 0.05 in each case). HBeAg-positive status was more common among those with coinfection (p = 0.01). However, compared to HBV/HIV coinfection, HBV monoinfected patients were consistently disadvantaged (Fig 1). HBV monoinfected patients were less likely to have been assessed by fibroscan (p < 0.0001), and less likely to be on antiviral therapy (p < 0.0001) compared to those with coinfection. The HBV monoinfected group were also more likely to have detectable HBV viraemia (p = 0.01), thrombocytopaenia (p = 0.01), elevated bilirubin (p = 0.002), and APRI score >2 (p = 0.02), compared to the coinfected group. Three cases of hepatocellular carcinoma were all in HBV monoinfection. Among 36 HBV monoinfected individuals not on therapy, 6 (17%) were treatment eligible based on local guidelines but had not been commenced on therapy.

Conclusion: Our results reflect systematic differences between management of HBV and HIV, and expose evidence of a consistent disadvantage for those with HBV monoinfection. This reflects late detection and referral to specialist services, and differences in guidelines. Enhanced advocacy, resources and infrastructure are required to optimise interventions for CHB.

FRI414

Clonal expansion of hepatocytes and state of hepatitis B virus DNA integration in patients with nucleos(t)ide analogue therapy

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Background and Aims: HBV DNA integration and hepatocyte clonal expansion are possible mechanisms of hepatocarcinogenesis. While it has been suggested that nucleos(t)ide analogues (NUCs) treatment can reduce the risk of hepatocellular carcinoma, the effect of NUC on HBV DNA integration has not been examined. This study aimed to investigate the effect of 1 year of NUCs treatment on HBV DNA integration and hepatocyte clonal expansion.

Method: This study included 10 chronic hepatitis B patients with paired liver biopsies collected before treatment and after 1 year of NUCs treatment. HBV DNA integration was detected by inverse PCR. Hepatocyte clone size, which reflects the extent of HBV DNA integration, was measured using a semi-quantitative end-point dilution method.

Results: All 10 patients (7 males and 3 females; mean age 38 ± 10 years) received entecavir treatment. Six were hepatitis B e antigen (HBeAg)-positive and 4 were HBeAg-negative at baseline. HBV DNA integration was detectable in all 10 patients at baseline. The viral junctions of HBV DNA integration clustered at the HBV direct repeat regions (nucleotides 1698 to 1986), while integration junctions at human chromosomes 1, 7, 8, 11, 16, 20 and 21 were identified. HBV DNA integration was also detected after 1 year of treatment, and the site of HBV DNA integration remained unchanged in each of the patients at year 1. There was no significant association between hepatocyte clone size and patients' age at baseline. After 1 year of treatment, a significant reduction in hepatocyte clone size was seen (median hepatocyte clone size at baseline vs. at year 1: 1.17 × 106 vs 1.48 × 105; P = 0.005), with a median reduction of 78% (range 21%–95%) in clone size. At year 1, serum HBV DNA, intrahepatic total HBV DNA and covalently closed circular DNA were reduced by 5.2 log, 1.5 log and 0.5 log respectively, but their reductions did not significantly correlate with the magnitude of hepatocyte clone size reduction.

Conclusion: HBV DNA integration was detected in patients both before and after 1 year of entecavir therapy. However, hepatocyte clone size, which reflects the degree of HBV DNA integration, was significantly reduced after 1 year of treatment. This suggested that, in addition to reducing serum and intrahepatic HBV DNA, NUCs

treatment by reducing the extent of HBV DNA integration, may have an additional anti-oncogenic mechanism.

FRI415

Machine learning identifies immune profile to predict virological relapse after stopping nucleos(t)ide analogue therapy in HBeAg negative chronic hepatitis B

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Background and Aims: Discontinuation of nucleos(t)ide analogue (NA) treatment in HBeAg negative patients with chronic hepatitis B is associated with a significant risk for virological relapse (VR). Currently, the virological and immunological background for relapse is poorly understood and there is a lack of predictors. This study investigated the use of soluble immune markers (SIMs) in predicting virological relapse (HBV DNA > 2,000 IU/ml).

Method: In a post-hoc analysis of a prospective, multicenter therapeutic vaccination trial (ABX-203, NCT02249988) HBsAg, HBcrAg, and 47 SIMs were repeatedly determined before NA was stopped. Forty-three non-cirrhotic HBeAg negative non-vaccinated patients were included. To detect the highest predictive constellation of host and viral markers a supervised machine learning approach was used.

Results: VR (HBV DNA ≥ 2,000 IU/ml) occurred in 27 of 43 patients. The predictive value for VR of single SIMs at time point of NA stop was

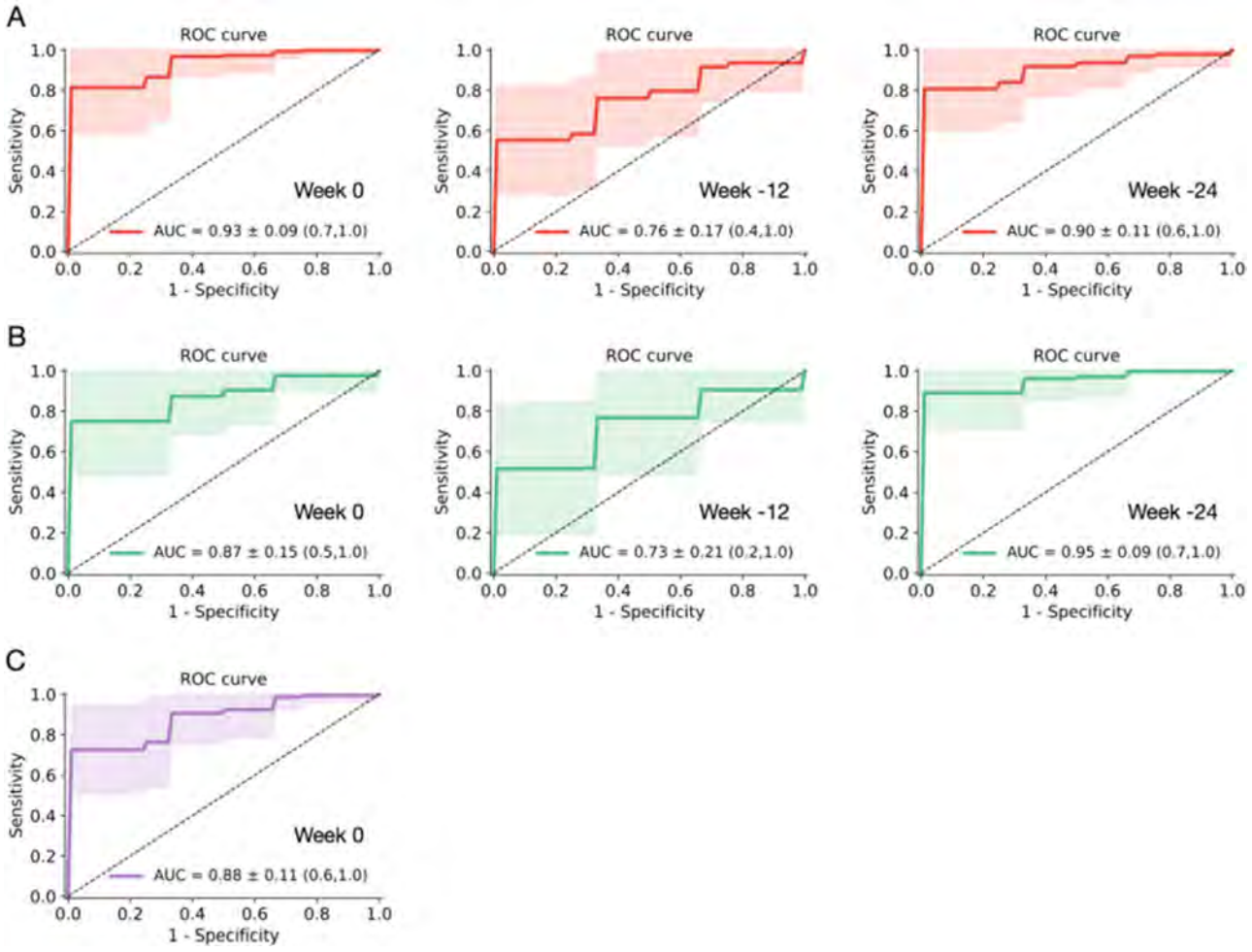

Figure: (abstract: FRI415): AUC values to predict virological relapse (HBV DNA ≥ 2,000 IU/ml) A) Sensitivity and specificity of 5 cytokines (IL-2, MIG, RANTES, SCF and TRAIL) at week 0, week -12 and week -24; B) Sensitivity and specificity of 4 cytokines and HBsAg (IL-2, RANTES, SCF, TRAIL and HBsAg) at week 0, week -12 and week -24; C) Sensitivity and specificity of 4 cytokines and HBcrAg (IL-2, RANTES, SCF, TRAIL and HBcrAg) at week 0, week -12 and week -24. IL-2: interleukin 2, MIG/CXCL9: monokine induced by gamma interferon, RANTES/CCL5: regulated on activation, normal T cell expressed and secreted; SCF: Stem cell factor, TRAIL: TNF-related apoptosis-inducing ligand.

best for IL-2, IL-17, and RANTES/CCL5 but with AUC of maximal 0.65. HBcrAg had a higher predictive power than HBsAg but lower than the SIMs. Applying a supervised machine learning algorithm allowed a remarkable improvement of relapse prediction. The combination of the five SIMs IL-2, MIG/CCL9, RANTES/CCL5, SCF, and TRAIL was highly reliable in predicting VR (0.93; 95% CI: 0.67–0.99). Predictive power of the cytokines remained high 12 and 24 weeks before treatment discontinuation (0.76, 0.48–0.99; 0.9, 0.56–0.99; respectively; Figure 1).

Conclusion: Host immune markers such as SIMs seem to be an underestimated marker for guiding treatment cessation in HBeAg negative CHB patients. Machine learning emerged as a valuable tool to predict SIM patterns that allow a precise identification of patients particularly suitable for NA cessation.

FRI416

Cessation of nucleos(t)ide analogues therapy in chronic hepatitis B: a systematic review and meta-analysis

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Background and Aims: To address the possibility of safe cessation of nucleos(t)ide analogues (NAs) therapy in chronic hepatitis B patients and to identify factors associated with off-NAs virological relapse (VR).

Method: A published work search was performed in order to identify all published studies including patients who discontinued NAs and were followed for ≥12 months. A systematic review and a meta-analysis were performed.

Results: Twenty-six studies involving 2573 patients who discontinued NAs were included. The pooled rate of off-NAs VR was 0,63, being lower in initially HBeAg-positive than HBeAg-negative patients (0.57 versus 0.62, P = 0.732). In view of the duration of follow up after NAs cessation, the pooled rates of VR were 0.47, 0.55, 0.61, 0.51, 0.73 and 0.64 at 6, 12, 24, 36, 48 and 60 months after NAs cessation, respectively, being relatively lower in initially HBeAg–positive (0.50, 0.55, 0.69, 0.57, 0.53, 0.68) than HBeAg-negative patients (0.31, 0.45, 0.55, 0.44, 0.48, 0.52) (P = 0.405). The pooled rates of biochemical relapse was 0.44, being lower in initially HBeAg-positive than HBeAg-negative patients (0.43 versus 0.48, P = 0.554). The pooled rates of hepatitis B surface antigen loss and seroconversion was 0.09 and 0.06, respectively. The pooled probabilities of VR at 12 months after NAs cessation were getting lower in studies defining VR by HBV DNA <200, <2000 and <20,000 IU/mL in all patients (0.80 versus 0.57 versus 0.39, P = 0.006) and initially HBeAg-negative patients (0.83 versus 0.68 versus 0.44, P < 0.001). The pooled rates of VR at 12 months after NAs cessation were significant different between duration of on-NAs virological response ≤24 months and >24 months in all patients (0.55 versus 0.41, P = 0.011), initially HBeAg-positive patients (0.59 versus 0.41, P = 0.031), and initially HBeAg-negative patients (0.53 versus 0.37, P = 0.025).

Conclusion: Safe cessation of NAs therapy seems to be feasible in a substantial proportion of CHB patients. On-NAs virological response >24 months reduces the risk of off-NAs VR.

FRI417

Prevalence of liver fibrosis in the natural course of chronic hepatitis B virus infection: a systematic review with meta-analysis

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Background and Aims: There still lack systematic quantitative data on the risk of liver fibrosis across the natural course of chronic HBV infection (CHB). We conducted meta-analyses based on systematic literature review, aiming to determine the prevalence of different fibrosis status, including non-fibrosis (NF), significant fibrosis (SF), advanced fibrosis (AF), and cirrhosis, in the phases of viral infection defined by current clinical practice guidelines (CPG) (EASL2017, APASL2016, and AASLD2016).

Method: The review followed the MOOSE guidelines. We searched Cochrane library, EMBASE, PubMed, SCOPUS, and Web of Science from 1/1/1993 to 9/30/2018 for literatures with histologic data on liver fibrosis in CHB natural course. CHB course was defined based on current criteria for identifying infection phases as recommended by the CPGs, including the HBeAg-positive immune-tolerant (P1) and immune-active (P2), HBeAg-negative immune-inactive (P3) and immune-reactive (P4), and HBsAg-negative (P5) phases. A common fibrosis index was applied to translate the scores used in diverse histologic systems into stages from F0-F4. NF was then defined by F0, SF by F2-4, AF by F3-4, and cirrhosis by F4. Pooled prevalence rate was

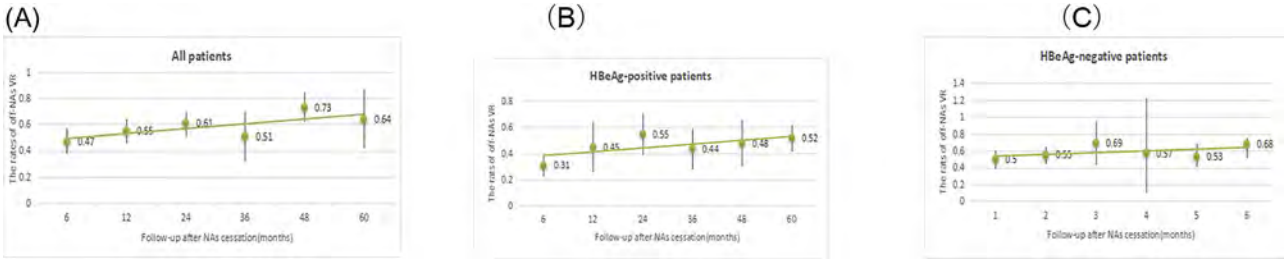

Figure: (abstract: FRI416): The rates of off-NAs virological relapse (VR) during follow-up after NAs cessation. Bars are 95% CI. Green lines are trend lines. (A) all patients,(B) HBeAg-positive patients, (C) HBeAg-negative patients.

Table 1: (abstract: FRI417): Estimated prevalence of fibrosis in CHB natural course

Phase	Patients number	Studies number	Basic characteristics				Fibrosis prevalence (%) (95% CI)			
			Age (years)	Male (%) (95% CI)	HBV DNA (IU/mL)	ALT (IU/L)	NF	SF	AF	Cirrhosis
P1	987	14	21.5–39.3	60.3 (55.6–65.0)	2.1×10^6–8.3×10^9	21–36	33.8 (19.6–47.9)	14.4 (8.5–20.3)	2.0 (0.1–3.9)	0.8 (0.0–1.6)
P2	4677	23	24.0–41.0	71.0 (67.5–74.4)	1.5×10^5–4.1×10^9	44–226	7.5 (4.5–10.5)	54.6 (46.8–62.4)	30.8 (24.1–37.4)	12.8 (8.7–16.9)
P3	2299	17	28.7–49.0	64.6 (59.7–69.4)	Negative to 7.1×10^3	19.3–40.0	29.8 (13.4–46.2)	20.5 (9.7–31.3)	5.7 (2.7–8.8)	3.3 (0.4–6.1)
P4	1740	16	28.7–48.0	77.6 (73.8–81.4)	10^4–1.3×10^7	50–119.6	5.9 (3.0–8.8)	52.9 (40.9–64.9)	33.1 (24.3–42.0)	11.6 (7.9–15.3)
P5[a]	15	1	36.0	73.3	Undetectable	Normal	0.0	40.0	20.0	20.0

[a]Without meta-analysis.

obtained from random-effects meta-analyses. Risks of bias were determined to identify quality of the studies.
Results: We identified 3,796 records by search strategy. A total of 41 eligible literatures were finally included. All had high-moderate quality. Of these, 9,718 adult participants from 13 countries were included in analyses, with 8,792 (90.1%) from Asia, 755 (7.8%) from Europe, 123 (1.3%) from US, and 82 (0.8%) from Africa. For each of the five phases, basic characteristics of participants and the estimated prevalence of NF, SF, AF, and cirrhosis were described in Table 1.
Conclusion: Fibrosis risk persists through CHB natural course. The present data can be used as supportive reference for clinical practice, guidelines complement, and investigation of non-invasive diagnosis.

FRI418
Estimating the clinical and economic burden of chronic hepatitis B (CHB) in the United States

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Background and Aims: Hepatitis B virus (HBV) infection is a major cause of chronic liver disease and hepatocellular carcinoma worldwide. Over the past decade, new antiviral therapies have been developed which can lead to sustained HBV suppression, potentially improving clinical outcomes and patient-reported outcomes (PROs). Our aim was to estimate the clinical and economic burden of prevalent CHB in 10,000 50-year-old patients in the United States.
Method: We used a decision tree combined with Markov model with 1-year cycles and 20-year horizon to estimate the burden of CHB when treated with nucleos(t)ide analogs (NAs). The cohort entered the model in one of four sub-states of CHB – E antigen positive/negative (HBeAg +, –) and high and low serum HBV DNA. We included a recovered state (R), compensated and decompensated cirrhosis (CC & DCC), and hepatocellular carcinoma (HCC), first year post-liver transplant (oyPLT) and post-liver transplant (PLT). Patients could die from liver-related and background mortality (LRM & BM). Following AASLD 2018 treatment guidelines, we treated patients with high viral load, and assumed patients were treatment naïve, received monotherapy, with 100% adherence over model horizon. Transition probabilities were found through literature review. For treatment probability, we used the combined market share for the three major NAs utilized in HBV care which was 85% (Trio Health). We estimated health state costs by micro-costing and through literature review in 2019 USD with 3% annual discount. Average annual treatment costs and average reduction in HCC incidence were weighted by market share of the NAs. We conducted a univariate sensitivity analysis.
Results: At 85% treatment probability, economic burden of CHB is $149.7 million over 20 years, or $884 per person-year, and 1.4 thousand person-years spent with HCC. When reducing the probability of treatment to 10%, economic burden increased to $189.6 million or $1,254 per person-year and 3.5 thousand person-years spent with HCC. When increasing probability of treatment to 95%, economic burden increased to $151 million, or $887 per person-year and 1.2 thousand person-years spent with HCC.

	Deterministic Analysis	Univariate Sensitivity Analysis	
Treatment Probability	85%	10%	95%
Total Costs of CHB	$149,735,221	$189,612,355	$150,965,312
Costs per Person-Year	$884.31	$1,254.05	$887.33
Person-Years with HCC	1,412	3,498	1,247
Total Person-Years Accumulated	169,324	151,200	170,134

Conclusion: These data suggest that the burden of CHB in the United States is driven by the incidence and costs of HCC and LT. Sensitivity analysis demonstrates that lower costs of treatment with a 10% treatment probability are offset by the increased incidence of HCC and associated costs, increasing costs per-person year by 42% even with decrease in total person-years accumulated by 11% due to high mortality rate of HCC.

Viral hepatitis C: Post SVR and long term follow up

FRI419
Exaggerated risk of vitamin B12 deficiency after HCV eradication with direct-acting antivirals

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Background and Aims: Elevated vitamin B12 levels have been considered as a predictive marker of acute and chronic liver disease of different etiologies. However, no reports have investigated the variation of vitamin B12 after the treatment of the underlying hepatic disease. Objetive: To evaluate the changes in vitamin B12 levels and the prevalence of its deficiency (vitamin B12 <180 pg/ml) after the eradication of HCV with direct-acting antivirals (DAA).
Method: Longitudinal prospective study including all treatment naive patients with DAA therapy for HCV eradication during the year 2018 in the Gastroenterology Department at the University Hospital Miguel Servet (Zaragoza. Spain). Basal vitamin B12 and homocysteine levels were analyzed and then, at the end of treatment, SVR 12, and SVR 48. This study was approved by our Institutional Review Board and all participants signed informed consent forms.
Results: 167 patients with HCV were included: 93 (58.12%) F1, 21 (13.12%) F2, 24 (15%) F3 and 22 (13.75%) F4. 52.7% were women. The median age was 53 years (range 20–87). Vitamin B12 levels (median [interquartile range]) decreased significantly during follow-up (323 pg/ml [246; 388] at baseline *vs.* 282 pg/ml [213; 344] in SVR48, p = 0.004). In turn, homocysteine tended t to increase (9.95 μmol/l [8.35; 11.7] baseline *vs.* 10.6 [9.13; 12.8] SVR48, p = 0.085).
The prevalence of vitamin B12 deficit increased significantly (3.1% baseline, 13.33% in SVR and 12% in SVR 48, (p = 0.009), while folic acid levels did not show significant changes during the follow-up (8.15 ng/mL [6.06; 11.4] *vs.* 7.50 [5.34; 10.4], p = 0.117).

Table 1: Vitamin B12, folic acid and homocysteine along the follow up.

Variable	Basal	SVR 48	P *
Median [interquartilic range]			
Vitamin B12 (pg/ml)	323 [246;388]	282 [213;344]	**0.004**
Homocysteine (μmol/l)	9.95 [8.35;11.7]	10.6 [9.13;12.8]	0.085
Folic acid (ng/mL)	8.15 [6.06;11.4]	7.50 [5.34;10.4]	0.117
B12 deficit (%)	3.1	12	**0.009**

*p-value for the media comparation (t-Student) or proportions (Chi^2).

Conclusion: DAA-treated patients have a progressive decrease in vitamin B12 levels after HCV eradication, with an increase in the prevalence of B12 deficiency one year after treatment. The

relationship of this decrease with the improvement of hepatic damage in patients with SVR is still unknown. However, given the clinical repercussions of vitamin B12 deficiency, routine monitoring of B12 is advised after DAA treatment.

FRI420

Risk of hepatocellular carcinoma recurrence in patients treated with direct acting antiviral therapy

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Background and Aims: The impact of direct acting antiviral (DAA) therapy on recurrence of HCC is controversial. In this study, we assessed rate and pattern of hepatocellular carcinoma (HCC) recurrence among DAA treated patients.

Method: This study included 392 patients with HCV-related HCC and complete response to resection, local ablation or transplantation, of whom 92 received DAA therapy for HCV, and followed up at a single tertiary referral center up to 30 months. HCC recurrence rates were calculated in DAA treated and untreated patients. Cox's regression analysis was used to identify risk factors associated with recurrent HCC among patients, and the pattern of HCC recurrence was compared in both groups.

Results: Baseline Child Pugh score (CTP), BCLC stage, HCC treatment modality, alpha-fetoprotein (AFP) level and platelet count were similar between DAA treated and untreated groups ($p > 0.05$). Follow-up after complete ablation was 155.8 person-years (PY) for DAA treated patients and 319.3 PY for DAA untreated patients. HCC recurred in 38 DAA-treated patients (41.3%) and 93 untreated patients (31%). The recurrence rate per 100 PY was 24.38 (95% CI, 17.7–33.5) for DAA treated patients vs. 31.01 (95% CI, 25.5–37.8) for untreated patients. The 1- and 2- year cumulative recurrence rates in the DAA cohort were 17.6% and 30.3%, compared to 28.3% and 48.3% in untreated patients, $p = 0.34$. Multivariate analysis showed that DAA therapy was not associated with increased HCC recurrence (adjusted HR = 0.91; 95% CI, 0.61–1.36), after adjustment for age, gender, CTP, AFP level, initial tumor burden, and HCC therapy. No difference in pattern of recurrences was noticed between both groups regarding size of recurrent tumor (30.8% of DAA treated recurrence vs 35.9%, of recurrence in DAA untreated patients were within Milan criteria; $p = 0.57$) or treatment received for recurrence (28.2% and 36.6% received potentially curative HCC therapy for recurrent HCC, $p = 0.34$). In patients treated with DAA, initial tumor diameter >3 cm was the only significant predictor of recurrent HCC.

Conclusion: In patients with complete response to HCC treatment, DAA therapy was not associated with increased recurrence rate. HCC recurrence patterns were similar in DAA-treated and untreated patients.

FRI421

Evidence of declining HCV transmission in Australia following scale-up of direct acting antiviral therapy

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Background and Aims: In Australia, DAAs have been funded by the Australian government since March 2016 for all adults living with chronic HCV. This unrestricted access has facilitated rapid uptake of treatment, with more than 70,000 people treated by the end of 2018 and with 50% coverage among people who inject drugs (PWIDs) who attended needle and syringe programs. Here we provide data that indicates this policy and rapid uptake of DAA therapy has led to a reduction in the number of new HCV infections in Australia.

Method: Since the early 1990s, it has been mandatory in Australia to notify any HCV diagnosis to state health departments who forward the information to the National Notifiable Disease Surveillance System (NNDSS). We extracted monthly HCV notification data from August 2009 to August 2019 from the NNDSS website and determined the existence of change points in trends using Poisson segmented regression. We report trends with a rate ratio (RR) and 95% confidence interval (95% CI). We used standard statistical methods to assess goodness-of-fit and evaluated the sensitivity of detected change points to outliers and the period of analysis.

Results: HCV notifications slowly increased from August 2009 followed by a sharp peak during 2016 and then a decline (Figure 1). We detected a changepoint in October 2016 (95% CI: July 2016, December 2016; $p < 0.001$) with the rate ratio changing from an increasing trend (RR 0·019; 95% CI 0·015–0·022; $p < 0.001$) before October 2016 to a declining trend (RR –0·086; 95% CI –0·10 to –0·072; $p < 0.001$) afterwards.

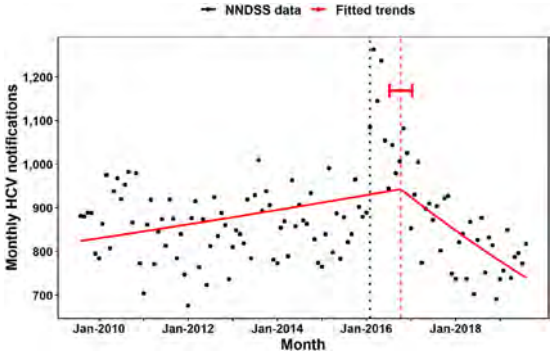

Figure: Monthly HCV notifications in Australia from August 2009 to August 2019 (black points: HCV notification data from National Notifiable Diseases Surveillance System (NNDSS), red line: segmented regression trend, vertical black-dotted line: subsidised DAA became available (1st March 2016), vertical red-dotted line: year of change point, red horizontal error bar: 95% CI for change point).

Conclusion: The short period of rapid increase in HCV notifications in early to mid-2016 is likely related to increased testing following the announcement in December 2015 of unrestricted DAA therapy access from March 2016. A degree of testing saturation among the at-risk population could be a contributor to the subsequent sharp decline, but we believe the continued decline indicates reduced new HCV infections. This is because the decline in notifications has coincided with continued high levels of HCV testing, and particularly high DAA uptake among PWID including people who are incarcerated.

FRI422

HIV co-infection is associated with lower risk of liver cancer after HCV-cure

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Background and Aims: In patients with active HCV infection, HIV accelerates liver disease progression. After SVR, HIV co-infection seems no longer impact on the risk of emergence of liver complications, considered as a whole. However, information about the effect of HIV co-infection on risk of specific liver complications after SVR is very limited. The aim of this study was to assess the impact of HIV infection on the risk of developing hepatocellular carcinoma (HCC) in HCV-infected patients who achieve SVR with direct-acting antiviral (DAA).
Method: Multisite prospective cohort study, where HCV-monoinfected patients and HIV/HCV-coinfected individuals were included if they met: 1) SVR with DAA-based combination; 2) Liver stiffness (LS) ≥9.5 kPa previous to treatment; 3) LS measurement at the SVR timepoint. The primary endpoint was the emergence of HCC. The relationship between the time to endpoint and the other variables was assessed in a multivariate analysis using a Fine-Gray regression model for competing risks. Propensity score (PS) for HIV infection was calculated with a logit model including variables which were significantly different in HIV+ and HIV- at baseline.
Results: 1006 HCV-infected patients were included, 661 (66%) coinfected with HIV. HIV/HCV-coinfected patients were younger (52 vs 56 years; p < 0.001), more frequently males (87% vs 73%; p < 0.001), and injecting drug users (84% vs 36%; p < 0.001). At SVR, a lower proportion of HCV-monoinfected patients showed MELD >10 (3% vs 7%; p = 0.041). After a median (Q1-Q3) follow-up time of 37 (23–42) months, 19 (1.9%) patients developed HCC [10 (2.9%) HCV-monoinfected, 9 (1.4%) HIV/HCV-coinfected individuals; p = 0.021]. In the multivariate analysis, HIV co-infection was associated with a lower adjusted risk of developing HCC [sHR = 0.27, 95% IC (0.09–0.83); p = 0.024]. Predictors of HCC emergence were: HCV genotype 3 [sHR = 5.7 (1.7–19.3); p = 0.005], MELD score at SVR [sHR = 1.45 (1.01–2.08); p = 0.042] and LS value at SVR [sHR = 1.03 (1.01–1.05) for 1 kPa increase; p = 0.015]. After adjusting the model by PS for HIV infection, HIV co-infection remained associated with lower risk of HCC [sHR = 0.28 (0.09–0.85), p = 0.025]. Stratifying by the median of PS, the association between HIV and HCC showed the same trend in the two categories created.
Conclusion: In HCV-infected patients with advanced fibrosis, who achieve SVR with DAA, HIV-coinfection is associated with a lower risk of HCC emergence. The underlying causes for this finding need to be investigated.

FRI423

Statins use corrects the impact of direct acting antiviral agents on lipid profile in hepatitis C virus patients

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Background and Aims: Hepatitis C virus (HCV) infection is associated with an increased risk of atherosclerosis, linked with alteration of the lipid profile. To date, few data are available regarding the impact of HCV clearance obtained with direct acting antiviral agents (DAAs) on lipid profile. DAAs therapy seems linked to an increase in total cholesterol (TC), LDL cholesterol and triglycerides (TG) suggesting a higher cardiovascular (CV) risk. We evaluated lipid profile changes after sustained viral response (SVR) with DAAs in dyslipidemic compared to non-dyslipidemic patients.
Method: Prospectively collected data of SVR patients were analyzed, with the exclusion of diabetic patients.
Results: 361 patients were enrolled and evaluated for a mean follow-up period (T1) of 10.6 ± 3 months. Mean age was 59,3 ± 11,1 years, with 55% males. 79 patients (21.9%) were dyslipidemic (63 were F1-F3 according to METAVIR assessed by transient elastography with FibroScan and 16 were F4) while 282 patients (78.1%) were non-dylipidemic (166 patients F1-F3 and 116 patients F4). At baseline, HCV genotype 2 was significantly more present in the dylipidemic group (p < 0.001). In the dyslipidemic group hypertension was more prevalent (p = 0.020), with a higher CV risk (p = 0.001) assessed by the SCORE system, more past CV events (30.4% vs 14.9%, p = 0.003), significant lower liver stiffness (p < 0.001) and, as expected, a significant higher level of TC, LDL and TG. No differences were found in transaminases and glicemic profile.
At T1, a significant improvement in ALT, AST, GGT and liver stiffness was found in all subgroups. In linear regression, the absence of significant changes in lipid profile was associated with statins use (p < 0,001, β = 2,3) in the dyslipidemic group. Regarding the non-dyslipidemic group, in the F1-F3 subgroup a worsening in TC (at T1 175.3 ± 29 mg/dl, p < 0.001), LDL (at T1 100.6 ± 26 mg/dl, p < 0.001) and TG (at T1 93.1 ± 40 mg/dl, p = 0.031) was found, while in the F4 subgroup only LDL reached a significant increase (at T1 87.7 ± 23 mg/dl, p = 0.040). No significant impact on HDL and glicemic profile was recorded.
Conclusion: In our cohort an impact on lipid profile was proved only in the non-dyslipidemic group after the use of DAAs, in particular with lower degrees of fibrosis. Interestingly, this increase did not reach the cut-offs considered dangerous for a worsened CV risk, but a longer follow-up is needed to confirm these results.

FRI424

Medium-term outcomes of hepatitis C virus-infected patients with a sustained viral response according to albumin-bilirubin grade

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Background and Aims: Owing to the development of direct-acting antiviral agents (DAAs), the rate of a sustained viral response (SVR) has dramatically improved. However, the previous studies did not fully evaluate the long-term prognoses of patients who achieve an SVR. We examined the incidence of hepatocellular carcinoma (HCC) and the survival of patients who achieved an SVR using the albumin-bilirubin (ALBI) grade*, a hepatic-function classification system useful for therapeutic decision making.
Method: Among 1,164 patients treated with DAAs from 2014 to 2019, 1,010 patients who achieved an SVR were prospectively evaluated. The median age of the patients was 68 (26–90) years, and 465 (46%) were males, 188 (19%) had cirrhosis, and 115 (11%) had a history of HCC treatment. The median follow-up period was 745 (92–1,690) days. The patients were stratified by ALBI grade at initiation of DAA therapy (1/2a/2b, 639/227/144). The cumulative rates of HCC and survival were calculated by Kaplan–Meier analysis and differences were evaluated by log-rank test. *Johnson PJ. *et al.* J Clin Oncol. 2015. Hiraoka A. *et al.* Liver Cancer 2017.
Results: Among patients with and without prior HCC, the cumulative rates of HCC were 37/2% at 1 year, 44/3% at 2 years, 49/6% at 3 years, and 63/9% at 4 years (p < 0.01). The survival rates were 94/99% at 2 years and 92/95% at 4 years. HCC recurrence was associated with a baseline alpha-fetoprotein level of >7 ng/mL, cirrhosis, and non-

surgical treatment for HCC, but not with ALBI grade. No clinical factor was related to survival at 4 years in patients with a history of HCC treatment. Among patients without prior HCC of ALBI grade 1/2a/2b, the cumulative rates of HCC were 1/4/3% at 1 year, 1/4/7% at 2 years, 3/6/16% at 3 years, and 3/9/26% at 4 years, respectively ($p < 0.01$). The survival rates were 99/99/96% at 2 years and 98/96/86% at 4 years, respectively ($p < 0.01$).

Conclusion: In patients with a history of HCC treatment, the rate of cumulative recurrence was almost 50% at 3 years, even if an SVR was achieved. However, there was no association between HCC recurrence and the prognosis at 4 years. In patients without prior HCC, the ALBI grade was capable of predicting HCC development and the prognosis after achieving an SVR.

FRI425

Identification of serum miRNAs whose expression were associated with and changed after HCV eradication

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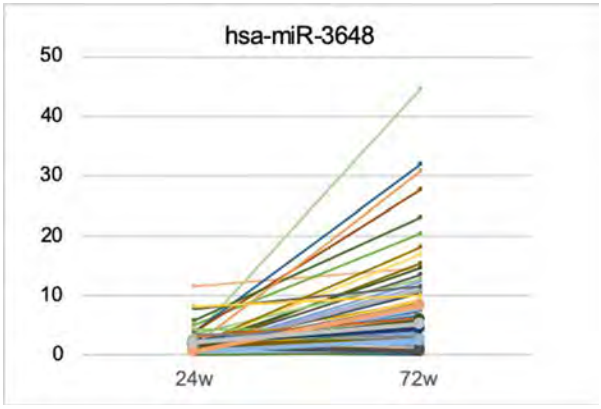
Background and Aims: Molecular and cellular machinery of wound healing in the HCV eradicated liver likely exerts influence on the persisting risk of hepatocellular carcinoma (HCC). As serum or plasma miRNA have been recognized as potential non-invasive markers for the activity and staging in chronic hepatitis C, they might be utilized also as surrogate for the multicellular process in the liver after sustained viral response (SVR), especially for its temporal evaluation. The aim of this exploratory study is to identify serum miRNA pattern in SVR patients and to evaluate its longitudinal changes.

Method: We recruited 217 patients who achieved SVR, but not with concurrent HCC diagnosis by imaging, at 24 weeks after the end of anti-viral treatment: 32 patients were considered as cohort 1, and remaining 185 were as cohort 2. RNA were extracted from the serum of cohort 1 at SVR24W or from those of 8 healthy volunteers and microarray hybridization was performed on Human miRNA array (TORAY, Japan). Normalization of raw intensity values, followed by analysis of data were performed using GeneSpring (Agilent Technologies, U.S.A.). We first extracted differentially expressed miRNAs (DEmiRs) in SVR 24W serum in cohort 1, compared with those in healthy volunteers, whose expression had FDR corrected $p < 0.05$ and a fold change (≥ 2) in signal intensity (unpaired Welch test). Next, validation of DEmiRs were performed by quantitative RT-PCR, using RNA that were extracted from the serum of cohort 2 at SVR24W or at SVR72W ($n = 93$), which were pre-mixed with cel-miR-39 as spike-in control.

Results: 44.9% of patients were predicted to be in advanced fibrosis, by their greater than 3.25 pretreatment FIB4 index. Among DEmiRs in cohort 1, overexpressed miR-3648 ($p = 0.0025$) and underexpressed miR-223-3p ($p = 0.0026$) were validated in cohort 2 by qRT-PCR. Steady-state level of both serum miRNAs were significantly increased at SVR72W from those at SVR24W ($p < 0.0001$). No DEmiRs at SVR24W were associated with either pretreatment FIB4 index, AFP values, or interferon free regimen.



Conclusion: Post SVR wound healing process in the liver may be monitored by serum miRNA pattern.

FRI426

Impact of genetic variants on liver disease regression in HCV patients with advanced chronic liver disease who achieved SVR to IFN-free therapies

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Background and Aims: Several single nucleotide variants (SNVs; including *PNPLA3 rs738409 C > G*, *TM6SF2 rs58542926 C > T*, *MBOAT7 rs641738 C > T*, and *HSD17B13 rs72613567 T > TA*) have been shown to promote or prevent progression to advanced chronic liver disease (ACLD) in patients with chronic hepatitis C (CHC). However, their influence on disease regression is unclear.

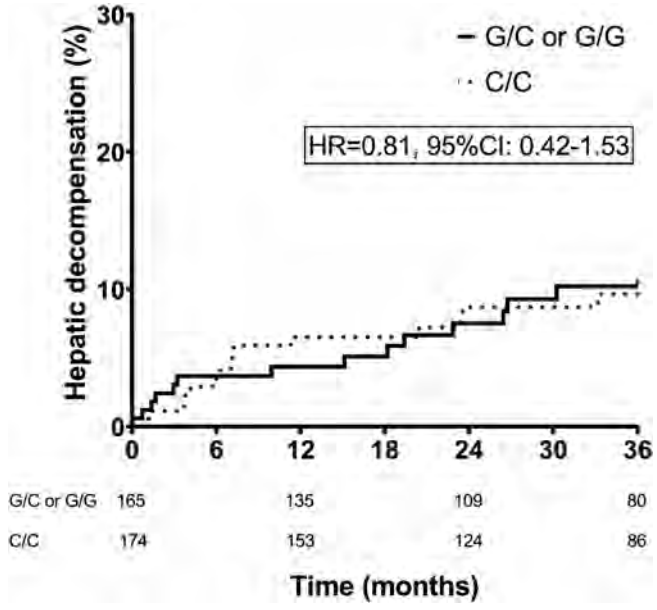
Therefore, we aimed to assess their impact on **(I)** the regression of portal hypertension, as assessed by hepatic venous pressure gradient (HVPG), **(II)** changes in non-invasive markers (transient elastography (TE) and von Willebrand factor (VWF)), and **(III)** clinical events in CHC patients with pre-treatment ACLD who achieved sustained virological response (SVR) to interferon (IFN)-free therapies.

Method: 339 CHC patients with pre-treatment ACLD (i.e., hepatic venous pressure gradient [HVPG]$\geq$6 mmHg and/or liver stiffness measurement [LSM]$\geq$10 kPa and/or advanced liver fibrosis/cirrhosis on histology) and information on the *PNPLA3 rs738409 C > G* variant were included into this retrospective analysis.

Results: Of 339 included patients, 49 (14.5%) had a history of hepatic decompensation (dACLD), while 290 (85.5%) had compensated ACLD (cACLD). Two hundred and ninety-seven (87.6%) patients were Child-Turcotte-Pugh (CTP) A. The mean MELD was of 8.8 ± 2.6 points, with a median LSM of 17.6 (11.8–28.0)kPa, median VWF levels of 243 (177–321)%, and a median VWF/platelet count ratio (VITRO) of 1.97 (1.13–3.38). Patients harboring the PNPLA3 *rs738409 G*-allele had more advanced liver disease prior to antiviral therapy, while liver disease severity was similar across the other SNVs.

In a subgroup of 88 patients with information on all SNVs and paired HVPG measurements, the distribution of *PNPLA3*, *TM6SF2*, *MBOAT7*, and *HSD17B13* genotypes was comparable between patients with vs. without an HVPG decrease.

In line with the observed changes in HVPG, treatment induced decreases in surrogates of portal hypertension (LSM, VWF, and VITRO) were comparable between carriers and non-carriers of the PNPLA3 *rs738409 G*-allele in the overall cohort.
Patients were followed for a median of 38 months after end of treatment. Interestingly, the PNPLA3 *rs738409 G*-allele did not impact hepatic decompensation or liver-related mortality in unadjusted analysis, or hepatic decompensation in an analysis adjusted for indicators of hepatic dysfunction and portal hypertension before treatment initiation.



Conclusion: Genetic variants in *PNPLA3, TM6SF2, MBOAT7, and HSD17B13* do not impact the regression of portal hypertension. After etiological cure (i.e., after SVR), the PNPLA3 *rs738409 G*-allele was also not associated with clinical events or mortality in our well-characterized cohort of ACLD due to CHC.

FRI428

HIV/HCV co-infected subjects show better thrombocytopenia improvement after sustained virologic response achievement than HCV mono-infected cirrhotics. Data from the hepaiCONA and PITER cohorts.

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Background and Aims: Thrombocytopenia (TCP) is common in HCV-related liver cirrhosis with portal hypertension (PHT). In HIV/HCV co-infected subjects it is due to several factors, including immune activation. After sustained virologic response (SVR), PHT shows an improvement in approximately 85% of cases but only one third returns to normality. Aim of present study is to compare TCP trend and return to normal values in co- and mono-infected cirrhotics after SVR achievement.
Method: HepaICONA and PITER are observational cohort studies that enroll patients undergoing treatment with direct acting agents throughout Italy. Subjects with a platelets (PLT) count <150,000 cell/mmc before DAA start who achieved SVR were selected. Demographic, clinical and laboratory features were collected. PLT count during and after DAA treatment was analyzed. Descriptive statistics, paired t and non-parametric (Chi-square and Kruskal-Wallis) tests were applied; KM probability curves and multivariable Cox regression models for PLT increase were used.
Results: 3,808 subjects were enrolled: 1,739 HIV/HCV co-infected from HepaICONA and 2,069 HCV mono-infected from PITER. Co-infected individuals were younger (53 versus 62 years, $p < 0.001$), with a higher median PLT count (173,000 versus 157,000, $p < 0.001$) and lower presence of TCP (36.4% versus 45.9%, $p < 0.001$). In the overall population, 12 months after SVR HIV+ showed a larger median PLT increase (15,930 versus 8,832 cell/mmc, $p < 0.001$). Among those with TCP, PLT count returned within normal values more commonly in co- than in mono-infected (35.1% versus 20.9%, $p < 0.001$). Figure 1 shows the probability for PLT increase assessed by mean of KM analysis: HIV+ subjects exerted a more favorable kinetics. After adjusting for confounding factors, HIV co-infection, baseline PLT and AST values and HCV genotype 3 were independently associated with TCP recovery.

Conclusion: PLT count returned within normal ranges in one third of co-infected and only in one fifth of mono-infected cirrhotics. PLT increase was more rapid and robust in HIV+ individuals: these data suggest that in this setting HCV eradication could have a stronger impact on the inflammatory milieu with a consequent better evolution of TCP. Nevertheless, SVR achievement failed to resolve TCP in the large majority of study population underlying the need for a careful and ongoing monitoring in subjects with PHT.

FRI429

Long-term liver fibrosis and outcomes in HCV-infected solid organ transplant recipients after DASSs-induced viral eradication

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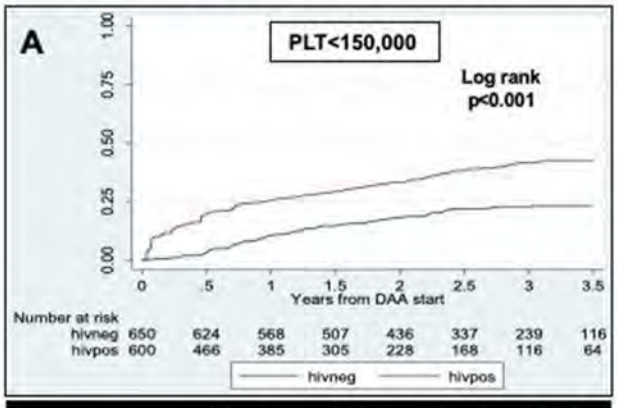
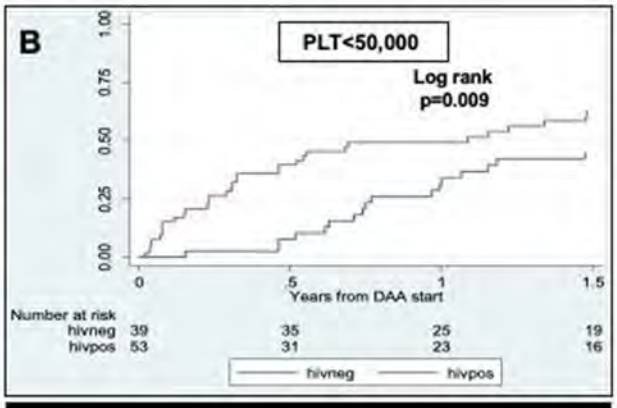
Background and Aims: Hepatitis C virus (HCV) infection is associated with faster liver fibrosis progression and higher mortality in solid organ transplant (SOT) recipients compared to non-transplanted population. High safety and efficacy of direct acting antivirals (DAAs) after SOT were reported worldwide. The aim of this study was to evaluate the long-term impact of viral eradication on fibrosis progression and patient survival after SOT.
Method: All consecutive HCV-infected patients treated with DAAs after SOT between August 2014 and January 2019 in a single transplant center in Italy were considered. Patients were either included in the NAVIGATORE platform or treated within the Compassionate Use Program. Clinical and virological features were registered at baseline and during the follow-up, at monthly intervals during treatment and at 3, 6, 12 months and 2, 3 years after end of treatment (EoT). Liver fibrosis was assessed by liver biopsy and/or transient elastography (TE) at baseline and during the follow-up.
Results: Overall, 110 patients treated with DAAs at median time of 44.5 months (IQR 13–111) after SOT (liver = 93, kidney = 14, heart = 1, heart-kidney = 1, liver-kidney = 1) were included. 55% of patients (n = 61) showed F3-F4 liver fibrosis at baseline. Median follow-up after DAAs was 47 months (IQR 31–54). Sustained virological response rate (SVR12) was 80% and 96% after retreatment. Patients who achieved SVR12 showed a significant improvement in biochemical tests from

Figure 1. Kaplan-Meier curves of platelets increase: probability to achieve a normal count (≥150,000 cell/mmc) in the thrombocytopenic population (**A**) and probability to achieve a count ≥50,000 cell/mmc in the subgroup with severe thrombocytopenia (**B**). Univariate and multivariate analyses of factors associated with platelets increase are shown below.





	HR	p	95%CI		AHR*	p	95%CI	
HIV+ (vs HIV-)	2.21	<.001	1.78	2.75	1.94	<.001	1.35	2.80
Baseline PLT, per 10,000 increase	**1.54**	**<.001**	**1.46**	**1.62**	**1.05**	**<.001**	**1.04**	**1.06**
HCV Genotype 3 (vs non-3)	**1.39**	**.015**	**1.06**	**1.80**	**1.46**	**.015**	**1.08**	**1.99**
Age, per 10 years older	0.80	<.001	0.72	0.89	0.92	.271	0.79	1.07
Males (vs Females)	1.19	.143	0.94	1.51	0.89	.390	0.68	1.16
LD/HCC/LT	**0.29**	**<.001**	**0.18**	**0.53**	**0.49**	**.028**	**0.30**	**0.93**
RBV use (vs non use)	0.75	.009	0.61	0.93	0.98	.855	0.75	1.27
Albumin <3.5 g/L (vs ≥3.5)	0.37	<.001	0.23	0.58	0.67	.107	0.41	1.09
ALT, per 10 U/L increase	1.00	.576	0.99	1.02	0.97	.059	0.94	1.00
AST, per 10 U/L increase	**0.96**	**.142**	**0.96**	**1.01**	**1.07**	**.001**	**1.03**	**1.11**
Total bilirubin >2 mg/dL (vs ≤2)	0.68	.068	0.46	1.03	0.79	.352	0.49	1.29

*Adjusted for all factors in table and also for number of PLT assessment post DAA start.

	HR	p	95%CI		AHR*	p	95%CI	
HIV+ (vs HIV-)	2.01	.011	1.18	3.44	1.85	.139	0.82	4.18
Baseline PLT, per 10,000 increase	**1.06**	**.005**	**1.02**	**1.11**	**1.09**	**<.001**	**1.03**	**1.15**
HCV Genotype 3 (vs non-3)	1.04	.907	0.57	1.89	0.77	.518	0.35	1.71
Age, per 10 years older	0.89	.472	0.65	1.22	1.40	.148	0.89	2.20
Males (vs Females)	1.42	.281	0.75	2.68	1.27	.526	0.61	2.67
LD/HCC/LT	0.58	.122	0.29	1.16	0.95	.911	0.38	2.40
RBV use (vs non use)	1.35	.298	0.77	2.37	1.03	.940	0.51	2.09
Albumin <3.5 g/L (vs ≥3.5)	0.69	.235	0.38	1.27	0.62	.202	0.30	1.29
ALT, per 10 U/L increase	1.64	.081	0.94	2.86	1.08	.131	0.98	1.20
AST, per 10 U/L increase	1.24	.502	0.67	2.29	0.96	.470	0.86	1.07
Total bilirubin >2 mg/dL (vs ≤2)	1.29	.416	0.70	2.39	2.36	.066	0.94	5.91

*Adjusted for all factors in table and also for number of PLT assessment post DAA start.

PLT: platelets count; LD: liver decompensation; HCC: hepatocellular carcinoma; OLT: liver transplantation; RBV: ribavirin; DAA: direct-acting agents.

Figure: (abstract: FRI428)

baseline to SVR48: bilirubin ($p < 0.001$), ALT ($p < 0.001$) and platelet count ($p = 0.006$). Overall, patients who achieved SVR12 showed an improvement in liver fibrosis measured by TE ($p < 0.001$) and APRI ($p < 0.001$) during the follow-up; this result was confirmed in cirrhotic patients ($p = 0.001$, $p < 0.001$). Patient survival at 12, 24 and 36 months after DAAs was 96%, 91% and 86%, respectively. Patients with F3-4 fibrosis before DAAs who achieved SVR12 had similar survival compared to patients with F0-2 ($p = 0.087$). Patients with F3-4 fibrosis before DAAs who relapsed, showed lower survival compared to the other groups ($p < 0.001$). At multivariate analysis, no variable considered was an independent risk factor for mortality after SOT.

Conclusion: Treatment with DAAs was effective after SOT. Long-term follow-up data demonstrated that viral eradication was associated with an improvement in hepatic function, liver fibrosis and post-SOT survival, even in patients with F3-4 fibrosis before DAAs.

FRI430

Development of hepatocellular carcinoma by patients aged 75 years or over after HCV elimination by all-oral DAA therapy: results from a large-scale, multicenter cohort study

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Background and Aims: Antiviral HCV therapy with direct-acting antivirals (DAAs) has become much easier than ever even for elderly patients. However, as much data as possible on the development of hepatocellular carcinoma (HCC) are needed to better manage HCC surveillance after HCV elimination. The aim of this study was to evaluate HCC development, including de novo and recurrence, and

the survival rate of Japanese chronic hepatitis C (CHC) patients aged 75–84 following the achievement of sustained viral response (SVR) by DAAs.

Method: This large-scale, multicenter cohort study included 726 consecutive patients with CHC aged 75–84 who achieved SVR by all-oral DAAs, divided into groups with (n = 578) or without previous HCC (n = 147). We excluded patients with decompensated cirrhosis, co-infection with HBV/HIV, or a history of organ transplantation. The Kaplan-Meier method and Cox proportional hazard analysis were used to calculate the cumulative HCC incidence and factors related to HCC.

Results: During the observational period (median: 38 months), the 1- and 3-year cumulative rates of de novo HCC were 2.3% and 6.2%, respectively. In multivariable Cox analysis, alpha-fetoprotein (AFP) at 12 weeks after the end of treatment (p12) (OR 1.01, P < 0.001) and high p12-FIB4 index (>3.25) (OR 2.08, P = 0.04) were extracted as predictors of de novo HCC. The 1- and 3-year cumulative rates of de novo HCC were 4.1% and 8.2% for patients with high p12-FIB4 index (>3.25), respectively (log-rank test: p < 0.01). For patients with prior HCC, the respective 1- and 3-year cumulative rates of HCC recurrence were 15.2% and 36.4% for patients treated with a curative procedure and 30.4% and 82.4% for patients treated with a non-curative procedure (log-rank test: both p < 0.001). The 3-year survival rates for the non-HCC, curative HCC, and non-curative HCC groups were 98.6%, 94.3%, and 67.3%, respectively. Liver-related complications, mainly HCC recurrence, were responsible for approximately 60% of all deaths for patients with previous HCC.

Conclusion: For older patients who achieved SVR, high p12-FIB4 index and p12-AFP were strongly associated with the development of de novo HCC. For patients with a prior history of HCC, HCC recurrence will commonly occur, even if curative HCC treatment has been received. However, the survival rates for the non-HCC and curative HCC groups were higher (over 90% in three years) than that of the non-curative HCC group.

FRI431

Deteriorated lipid profiles and cardio-cerebrovascular events after hepatitis C virus eradication

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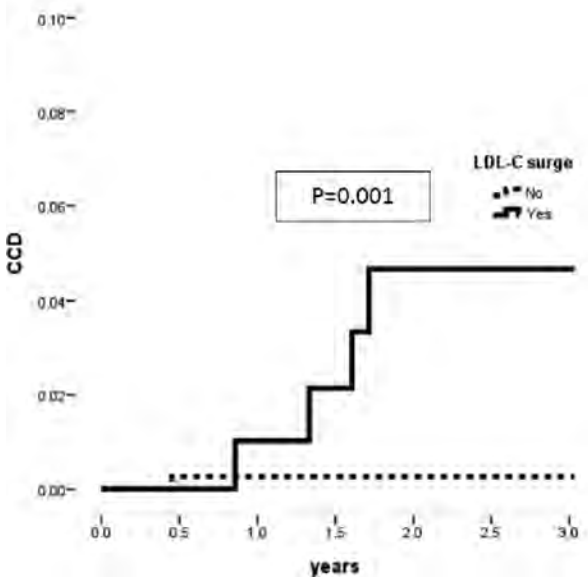
Background and Aims: Chronic hepatitis C virus (HCV) infection is associated with lower levels of total cholesterol (T-CHOL) and low-density lipoprotein cholesterol (LDL-C). Whether viral eradication leads to dyslipidemia and increases the risk of cardio-cerebral disease is unclear among chronic hepatitis C (CHC) patients after therapy with direct-acting-antivirals (DAAs).

Method: Lipid profiles were measured throughout DAA therapy and annually thereafter in CHC patients with a sustained virological response (SVR, undetectable HCV RNA at posttreatment week 12). The primary end-point was the occurrence of the events.

Results: A total of 617 SVR patients were included, with a mean follow-up period of 26.8 months (range:1–65 months). T-CHOL and LDL-C levels increased significantly from treatment week-4 to 2 years after treatment. A significant increase in the triglyceride level was noted at/after the end-of-treatment, whereas a significant increase in high-density lipoprotein cholesterol was observed only until 12 weeks after the end-of-treatment. Logistic regression analysis revealed that factors independently associated with a significant cholesterol increase included age (odds ratio [OR]/95% confidence intervals [CI]:1.02/1.006–1.039, P = 0.007) and smoking (OR/CI:3.21/1.14–9.02, P = 0.027). Five patients developed cardio-cerebral diseases during the follow-up period (36 per 1000 person-years). Compared to patients without vascular events, a significantly higher proportion of those with vascular events experienced an LDL-C surge >40% (80% vs. 19.9%, log-rank test P = 0.001). Cox regression analysis revealed that an LDL-C surge >40% was the only factor predictive of vascular events (HR/CI: 15.44/1.73–138.20, P = 0.014).



Conclusion: Dyslipidemia occurred after HCV eradication, which was associated with the risk of cardio-cerebrovascular diseases. Attention should also be paid to the extrahepatic consequence beyond liver-related complications in the post-SVR era.

FRI432

Dynamic of cytokine profiles predicts risk of HCC among HCV patients with advanced fibrosis after successful antiviral therapy

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Background and Aims: Successful HCV eradication did not eliminate HCC development among patients with advanced fibrosis. Clearance of HCV by DAA or IFN results in reconstitution of immune surveillance. We aimed to investigate the impact of differential cytokine expression on the development of HCC following antiviral therapy.

Method: 50 HCV patients with advanced fibrosis receiving pegIFN/RBV and 50 age-, sex- and fibrosis-matched HCV patients receiving DAA who achieved sustained virologic response (SVR) were enrolled in this study. The primary endpoint is the development of HCC. Cytokines profile were measured at baseline and SVR12 or SVR24 follow-up. A total of 64 cytokines was detected by the multiplex immunoassay.

Results: HCC developed in 12 (IFN group n = 11, DAA group n = 1) of the 97 patients over 459 person-years of follow-up after HCV eradication. In univariate analysis, the variation of tumor necrosis factors (TNF)-α and TWEAK (TNF-like weak inducer of apoptosis) after antiviral therapy were significantly associated with the development of HCC. The multivariate Cox regression model showed the reduction of TNF-α ($\triangle$ = –5.7 pg/ml) was the independent risk factor of HCC (HR = 11.54, 95% C.I. = 2.27–58.72, p = 0.003). We established an HCC predictive model as follows: Score = 5 × Gender (male = 1, female = 0) + 8 x$\triangle$TNF ($\leqq$–5.7, yes = 1, no = 0) + 11 x$\triangle$TWEAK ($\leqq$–70, yes = 1, no = 0). Time-dependent ROC analysis

revealed the 3-year, 5-year, 10-year, and 13-year AUC were 0.815, 0.836, 0.870, and 0.916, respectively.
Conclusion: Reduction of TNF-α after antivirals predicts HCC development in chronic hepatitis C patients with advanced fibrosis after successful viral eradication.

FRI433
Procoagulant imbalance in patients with non-cirrhotic chronic hepatitis C (CHC) improves six months after eradication with direct-acting antiviral agents (DAAs) and likely correlates with liver fibrosis

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Background and Aims: Chronic hepatitis C (CHC) is one of the most important causes of morbidity and mortality not only for the liver but also for cardiovascular diseases. A procoagulant imbalance, potentially responsible for cardiovascular disease and liver injury, has been reported in patients with CHC without cirrhosis. Aim: to assess whether HCV eradication by DAAs leads to a reduction in the procoagulant imbalance in CHC patients without cirrhosis and correlates with the improvement in hepatic histology.
Method: From 2017 to 2019, 122 patients with non-cirrhotic CHC (mean age 58.9 ± 10.5 years), were enrolled. Clinical and biochemical parameters, presence of steatosis (ultrasound), severity of liver damage [liver stiffness measurement (LSM) and non-invasive fibrosis scores (FIB-4 and NAFLD fibrosis score (NFS))] and coagulation balance through the evaluation of endogenous thrombin potential (ETP) with/without thrombomodulin and protein C (PC) – factor VIII ratio, were determined at enrollment and at 6 ± 1 months after sustained virological response (SVR) confirmation. Coagulation parameters of CHC patients at baseline were compared to those of 188 control subjects, enrolled among healthy hospital employers.
Results: Indexes of procoagulant imbalance were significantly higher in CHC patients than in controls (FVIII/PC ratio 1.7 + 0.7 vs 1.1 + 0.3; ETP ratio 0.8 + 0.1 vs 0.6 + 0.2, $p < 0.0001$). Pre-treatment indexes of procoagulant imbalance (FVIII/PC ratio) at analysis adjusted for sex, BMI, diabetes and GGT was significant associated with FIB4 (Coefficient 0.6, SE 0.2, $p = 0.003$) and NFS (coefficient 0.7 SE 0.1, $p < 0.0001$). Six months after SVR we observed a significant reduction in the procoagulant imbalance compared to what was observed before treatment (FVIII/PC 1.3 ± 0.5 vs 1.6 ± 0.6, ETP ratio 0.64 ± 0.11 vs 0.73 ± 0.1, $p < 0.0001$) and a decrease of liver fibrosis compared to pre-treatment (LSM 5.1 ± 1.7 vs 6.5 ± 5.5; NFS 0.1 ± 1.9 vs – 1.9 ± 1.2; $p < 0.0001$ and FIB4 1.9 ± 1.2 vs 1.6 ± 0.7, $p = 0.02$). At analysis adjusted for sex, BMI, diabetes, and GGT, the FVIII/PC was significantly associated with FIB4 (adjusted-coefficient 0.3, SE 0.14, $p = 0.01$) but not with LSM and NFS.
Conclusion: The viral eradication induced by DAA leads to a reduction in the procoagulant imbalance in non-cirrhotic patients with CHC. Whether this mechanism underlies the reported reduction of fibrosis after SVR needs to be confirmed in a larger cohort of patients with a longer follow up.

FRI434
Direct-acting antivirals improve treatment outcomes in patients with chronic hepatitis C-related hepatocellular carcinoma treated with transarterial chemoembolization: a nationwide, multi-center, retrospective cohort study

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Background and Aims: The influence of direct-acting antivirals (DAAs) for chronic hepatitis C (CHC) on hepatocellular carcinoma (HCC) is controversial. We investigated whether eradicating CHC using DAAs influenced treatment outcomes in patients with CHC-related HCC, treated with transarterial chemoembolization (TACE).
Method: In this nationwide, multi-center, retrospective cohort, patients with CHC-related HCC who were treated with TACE as the first anti-cancer treatment and who achieved a sustained virological response (SVR) using DAAs (DAA group) were recruited between 2006 and 2017. Patients with a SVR using the interferon-based treatment (IFN group) and those without treatment (Control group) were also recruited for comparison.
Results: In total, 425 patients were eligible for the study. Of these, 356 (83.8%), 26 (6.1%), and 43 (10.1%) patients were allocated into the Control, IFN, and DAA groups, respectively. A multivariate analysis showed that liver cirrhosis, segmental portal vein thrombosis, and larger maximal tumour size independently predicted an increased risk of progression (all $p < 0.05$), whereas the DAA group (vs. IFN and Control group) independently predicted a reduced risk of progression (hazard ratio = 0.630, 95% confidence interval 0.411–0.966, $p = 0.034$). The cumulative incidence rate of HCC progression in the DAA group was significantly lower than that in the IFN and Control groups ($p = 0.033$, log-rank test). In addition, the DAA group (vs. IFN and Control group) was independently associated with a reduced risk of mortality ($p = 0.042$).

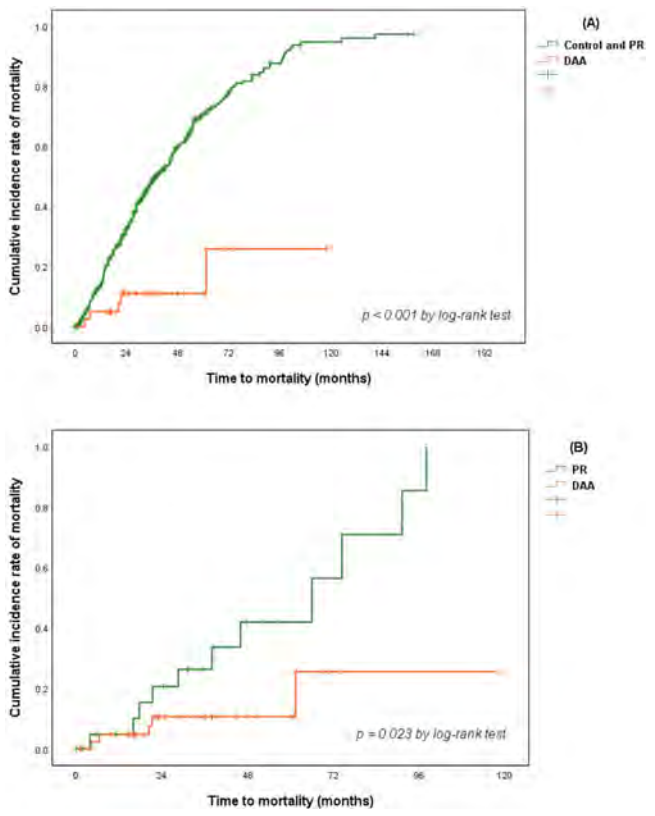

Figure 3 The cumulative incidence rate of mortality (A) Control and PR vs. DAA, (B) PR vs. DAA.

Conclusion: DAA treatment provided significantly prolonged progression-free survival in patients with CHC-related HCC treated with TACE, compared to IFN treatment or no treatment.

FRI435

Patients treated for hepatitis C: an observational study with the French administrative healthcare database (SNDS)

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Background and Aims: In 2014 direct antiviral agents (DAA) became available for the treatment of chronic hepatitis C (CHC) for patients with severe fibrosis in France. In 2017, the universal access to DAA was adopted by the French health minister. The aim of this study is to evaluate the impact of DAAs on access to CHC treatment and HCV screening.
Method: All patients affiliated to the French national health insurance, screened or treated against CHC between 2015 and 2018 were included and followed. Different algorithms were developed to identify special populations: migrants, prisoners, HIV+ patients, psychiatric patients, and drug users.
Results: Over the study period 2015–2017, 51,478 patients were treated against CHC (mean age 55.5 years; min: 18 years; max: 95 years; q1: 49 years; q3: 62 years; CI 95%: 55.4–55.6 years, 59.8% of males). Between 2015 to 2017, the annual treated population increased by 30% (17,400 to 22,700 patients), the mean age decreased from 57 to 54 years and the percentage of female increased from 35% to 45%. The weight of HIV+ patients dropped from 18% to 8% of the patients treated with DAA, while for the populations, an increase or stabilization was observed: 3% to 5% for migrants, 1% to 5% for prisoners, 21% to 20% for psychiatric patients, and 16% to 19% for drug users. The population of screened patients increased by 11% between 2015 and 2017 (2.8 to 3.1 million patients). The median delay between the last screening test and the treatment initiation decreased from 187 days in 2015 to 86 days in 2017 and 43 days in 2018.
The results for the year 2018 will be presented at the conference, with the poster.
Conclusion: This study highlights the impact of providing universal access to DAA with an increase of patients treated in 2017, of the screened population and the reduction of time between screening and treatment initiation. This is also the first study from SNDS data using algorithms to identify special populations.

FRI436

Role of pre- and post-treatment transient elastography measurements in predicting hepatocellular carcinoma (HCC) among hepatitis C patients treated with direct acting antivirals (DAAs)

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Background and Aims: Current guidelines recommend regular lifelong HCC screening in HCV patients with advanced fibrosis or cirrhosis. However, no study has evaluated the impact of early changes in liver stiffness measurement (LSM) by transient elastography (TE), which may reflect DAA-induced improvement in liver inflammation, on subsequent HCC risk after successful eradication of HCV. Therefore, we evaluated the association between LSM measured by TE pre- and early post-DAA treatment, and HCC occurrence.
Method: All electronic medical records of HCV patients treated with DAA at the University of Calgary Liver Unit (UCLU) between January 2014 and December 2017 were reviewed (n = 1,161) to identify those patients who developed HCC after completing treatment. Patients were excluded if they were treated for HCV while having HCC, or developed HCC during or immediately after (within 3 months) therapy. Baseline LSM was defined as TE within 6 months before starting DAA therapy, and post-treatment LSM was defined as TE within 36 months post-DAA therapy. We used Cox regression analysis to evaluate the association between pre- and post-HCV treatment TE measurements and HCC occurrence. We adjusted for age, sex, HCV genotype, and Charlson comorbidity index in our models.
Results: We identified 524 patients with a valid TE assessment obtained both at pre- and post-DAA treatment. In our cohort, median TE pre-DAA treatment was 12.1 kPa (IQR: 8.3–21.1 kPa), while post-DAA TE was 8.4 kPa (IQR: 5.8–14.1 kPa), $p < 0.001$.Therefore, the majority of our cohort (65.1%, n = 341) had advanced fibrosis or cirrhosis (TE >9.5 kPa) pre-DAA treatment, compared to 43.5% (n = 228) post-treatment. Within a median follow-up of 26 months (IQR:14–36) 18 patients (3.4%) developed HCC. In our cohort, sustained viral response (SVR) was 98.6% and all HCC patients had achieved SVR. Patients who developed HCC were similar to those not developing HCC according to sex (male 72.2% vs. 61.0%), age (median: 61 vs. 59 year), HCV genotype (1a: 38.9% vs. 49.4%), and having >2 comorbidities (66.7% vs. 58.3%), respectively; $p > 0.05$ for all comparisons. However, patients who developed HCC had a higher median TE pre-treatment (29.2 vs. 12.0 kPa, $p < 0.001$) and post- treatment (15.8 vs. 8.1 kPa, $p < 0.001$), respectively. All patients who developed HCC had TE >9.5 kPa at pre-treatment, while one (5.6%) patient had a post-treatment TE <9.5 kPa. In our adjusted Cox regression models, pre-treatment TE >9.5 kPa accurately predicted HCC (all HCC patients had pre-treatment TE>9.5 kPa), while post-treatment TE of >9.5 kPa was a strong predictor for HCC (HR: 18.70, 2.46–141.92).
Conclusion: In our large DAA-treated HCV cohort, pre- and post-treatment TE indicating advanced fibrosis or cirrhosis were strong predictors for HCC development post-treatment. Future studies should examine utility and cost effectiveness of measuring LSM post-HCV therapy on HCC occurrence.

FRI437

Non-invasive tests predict the risk of hepatocellular carcinoma in hepatitis C patients after sustained virological response: impact on HCC surveillance

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Background and Aims: After achieving the sustained virological response (SVR), hepatitis C (HCV) patients showing cirrhosis or advanced fibrosis (>10 kPa) must be screened from hepatocellular carcinoma (HCC) twice a year (EASL CPG, 2018). We assessed the role of non-invasive tests (NITs) [FIB4 and APRI] on HCC prediction and need for surveillance after SVR in patients treated with direct-acting antivirals (DAA).

Method: Multicenter study including 1180 Hepatitis C patients reaching SVR after DAA therapy. Patients suffering HCC within six months from starting DAA therapy (n = 5), as well as HCC and liver transplant before treatment, were excluded. They were followed-up to 5 years (36 ± 15 months) or until HCC occurrence (liver transplant and death before HCC were competing events).

Results: The 76% (898/1180) of the cohort had EASL criterium for HCC screening (cirrhosis or >10 kPa after SVR). HCC occurred in 5% (63/1180) of patients, while 1% (12/1180) was transplanted and 5% (61/1180) died before HCC diagnosis. Male sex [sHR 1.84 (95%CI 1.02–3.29); p = 0.041], cirrhosis [sHR 4.91 (95%CI 1.69–14.3); p = 0.004], albumin [sHR 0.51 (95%CI 0.32–0.83); p = 0.007], FIB4>3.25 [sHR 2.58 (95%CI 1.38–4.81); p = 0.003] and APRI>1.5 [sHR 2.29 (95%CI 1.33–3.93); p = 0.003] predicted HCC. Figure shows HCC rate per 100 persons-year, and HCC and mortality cumulative incidence, depending on baseline FIB4 and APRI. Pre- and post-treatment FIB4>3.25 [OR 10.86 (95%CI 3.06–38.53); p < 0.0001] and APRI>1.5 [OR 18.78 (95%CI 4.97–70.95); p < 0.0001] showed the highest HCC risk.

Conclusion: Combination of NITs predicted HCC risk and mortality after SVR in hepatitis C patients showing cirrhosis and/or baseline transient elastography >10 kPa. Subjects with FIB4<3.25 and/or APRI<1.5 had a low HCC risk, so surveillance could be not cost-effective. By contrast, patients with FIB4>3.25 and APRI>1.5 belonged to a high-risk group and should be included in a routine surveillance program.

HCC per 100 persons-year						
EASL criterium for HCC screening	FIB4<3.25	FIB4>3.25	APRI<1.5	APRI>1.5	FIB4<3.25 & APRI<1.5	FIB4>3.25 & APRI>1.5
No	0.02	0.07	0.02	0.09	0.02	0.13
Yes	0.11	0.28	0.14	0.30	0.11	0.31
HCC annual incidence (%)**						
Year	FIB4<3.25	FIB4>3.25	APRI<1.5	APRI>1.5	FIB4<3.25 & APRI<1.5	FIB4>3.25 & APRI>1.5
First	1.05	4.1	1.45	4.02	1.40	4.31
Second	0.31	1.66	0.42	1.77	0.40	1.91
Third	0.61	2.57	0.70	2.87	0.67	3.08
Fourth	0.35	2.33	0.58	2.54	0.56	2.69
Fifth	0.56	1.56	0.44	2.07	0.44	2.13
HCC 1-year cumulative incidence (CI) (%)						
EASL criterium for HCC screening	FIB4<3.25	FIB4>3.25	APRI<1.5	APRI>1.5	FIB4<3.25 & APRI<1.5	FIB4>3.25 & APRI>1.5
No	0.4	0	0.4	0	0.4	0
Yes	1.4#	4.4#	2@	4.3@	1.9$	4.6$
HCC 5-year CI (%)						
EASL criterium for HCC screening	FIB4<3.25	FIB4>3.25	APRI<1.5	APRI>1.5	FIB4<3.25 & APRI<1.5	FIB4>3.25 & APRI>1.5
No	0.8#	2.9#	0.8@	3.2@	0.8$	4.3$
Yes	2.9#	10#	3.8@	10.5@	3.6$	11.1$
Mortality 5-year CI (%)						
EASL criterium for HCC screening	FIB4<3.25	FIB4>3.25	APRI<1.5	APRI>1.5	FIB4<3.25 & APRI<1.5	FIB4>3.25 & APRI>1.5
No	0.8#	3.3#	0.8@	5.5@	0.8$	8.3$
Yes	5.7#	11.6#	6.3@	10.9@	5.4$	11.2$

** Cost-effective screening: 1.5% HCC annual incidence (Kanwal. Hepatology 2019)

# p<0.05 FIB4 <3.25 vs FIB4 >3.25

@ p<0.05 APRI <1.5 vs APRI >1.5

$ p<0.05 FIB4<3.25 & APRI<1.5 vs FIB4>3.25 & APRI>1.5

Figure: (abstract: FRI437)

FRI438

Reinfection with hepatitis C following cure: results from the TraP Hep C program in Iceland - a prospective nationwide, population-based study

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Background and Aims: The introduction of direct-acting antivirals (DAAs) has revolutionised treatment of hepatitis C but reinfections among those who share injection drug paraphernalia can jeopardize efforts to eliminate HCV infection as a public health threat. Risk of reinfection has been reported to be higher among younger patients and those who mainly use stimulants. The Treatment as Prevention for Hepatitis C in Iceland (TraP Hep C), was started in 2016 in Iceland, offering treatment with DAAs to all HCV-infected individuals. We sought to determine the incidence of HCV reinfections among patients in the program.

Method: Background clinical data was gathered prospectively. The study cohort was limited to patients who completed treatment and achieved sustained virological response (SVR) between January 11th 2016–November 20th 2018, and thus had >1 year of observation following cure. In addition, viral genotypes and viral deep sequencing results were reviewed. The observed follow-up time from confirmed SVR to the most recent HCV PCR was used to calculate the period for each individual and the reinfection rate/100 person- years (PYs) for the patient cohort. In addition, to account for low-risk patients in the cohort we also approximated the theoretical minimum reinfection rate, by the assumption that every patient with last HCV PCR listed as negative had remained negative until November 20th 2019.

Results: A total of 617 treatments of 597 patients (409 males, average age 44,5 years) were completed with confirmed SVR. During follow-up, 44 reinfections occurred in 42 patients (9 female, 33 male). The total follow-up was 494,7 PYs with an average time to a positive HCV PCR test of 380 days. History of IDU was reported by 508 (85%) and recent IDU with 205 (33%) treatments. Stimulants were the preferred iv drug among 85%. The observed overall reinfection rate was 8,9/100 PYs (95% CI 5.8–13.6). High reinfection rates were associated with homelessness (24,3/100 PYs), recent IDU (reinfection rate 18,1/100 PYs), concomitant IDU and use of non-intravenous stimulants (reinfection rate 26,2/100 PYs), and young age (20–24 years; reinfection rate 24/100 PYs). The theoretical (calculated) observation period for the total cohort was 1502 PYs and thus the lowest theoretical minimum reinfection rate in Iceland was 2,9/100 PYs (95% CI 1,9–4,5). Most reinfected patients have been successfully retreated.

Conclusion: The observed reinfection rate after successful DAA treatment in Iceland is high and seems to be segregated to young marginalized people who continue to use drugs and those who have unstable housing. The inherent bias towards repeat blood tests in high-risk patients may lead to an overestimate of reinfection rates. Further emphasis on people at the highest risk of reinfection is challenging, but essential in order to maintain the effectiveness of treatment and further reduce HCV transmission.

FRI439

Targeting clinical epigenetic reprogramming for chemoprevention of metabolic and viral hepatocellular carcinoma

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Background and Aims: Chronic hepatitis C (CHC) and non-alcoholic steatohepatitis (NASH) are major underlying etiologies for hepatocellular carcinoma (HCC), one of the fastest growing cause for cancer-related mortality. However, options for treating HCC are unsatisfactory with absent chemopreventive strategies. We have recently shown that chronic HCV infection results in epigenetic modifications that drive HCC development and persist after DAA cure in patients with CHC (Hamdane, Juehling et al. Gastroenterology 2019). Here we aimed to investigate hepatocyte chromatin readers and modifiers as targets for HCC chemoprevention in CHC and NASH-induced liver disease.

Method: Liver tissues samples from CHC and NASH patients with early and late stage disease were analyzed using genome-wide RNA-seq and ChIPmentation-based ChIP-Seq of the H3K27ac histone modification. CHC- and NASH-specific epigenetic modifications and transcriptional reprogramming were modeled in human liver cell culture systems and animal models. Perturbation studies combined with small molecule screens followed by *in vivo* and *ex vivo* validation were applied to identify chromatin modifiers and readers for HCC chemoprevention.

Results: CHC and NASH share a redundant set of epigenetic and transcriptional modifications inducing a transcriptional program driving carcinogenesis in the liver of patients. Using a cell-based system modeling the virus and NASH-induced epigenetic modifications in patients, we identified chromatin readers as targets to revert liver gene transcription driving clinical HCC risk. Proof-of-concept studies in a NASH-HCC mouse model showed that the pharmacological inhibition of chromatin reader BRD4 inhibited liver disease progression and hepatocarcinogenesis by restoring transcriptional reprogramming of the genes that were epigenetically altered in patients.

Conclusion: Our epigenetic and transcriptional analyses suggest that CHC and NASH share common mechanisms of disease progression and HCC risk. Our perturbation studies in cell culture and animal models uncover the functional relevance of metabolic and virus-induced epigenetic alterations for HCC risk. Our pharmacological *in vivo* studies identify chromatin readers are candidate targets for HCC chemoprevention in patients with chronic liver disease.

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Simple blood test criteria for non-cirrhosis plus age and post-treatment AFP rule-out the risk of hepatocellular carcinoma development after SVR

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Background and Aims: The EASL guideline suggest that patients without advanced fibrosis or cirrhosis could be discharged after sustained virologic response (SVR). Simplified HCV treatment algorism for treatment-naive patients without cirrhosis by AASLD/IDSA also advised against liver-related follow-up after SVR for no-cirrhotic patients. In this algorism, any positive result with the cutoffs of the following was used to suggest cirrhosis: FIB-4 >3.25, Platelet count <150,000/mm^3, APRI >2.0, and Fibroscan stiffness >12.5 kPa. The aim of the present study was to validate these cutoffs in terms of hepatocellular carcinoma (HCC) risk after SVR, and to further refine the criteria of patients who could be discharged after SVR.
Method: A hospital cohort of 717 patients who had no prior history of HCC and achieved SVR by interferon-free DAA regimens were studied. The incidence of HCC development was analyzed after stratification by the number of positive test results for FIB-4 >3.25, Platelet count <150,000/mm^3, and APRI >2.0. In patients with no-cirrhosis, factors for HCC risk was analysed.
Results: The number of patients with 1, 2, and 3 positive tests was 125 (17.4%), 160 (22.3%), and 5 (0.7%), respectively. Thus, a total of 40.4% was regarded as cirrhosis. The remaining 427 patients (59.6%) with no positive results were regarded as no-cirrhosis. During the median observation of 2.3 years after SVR, HCC developed in 27 patients. The incidence of HCC in patients with cirrhosis was significantly high compared to no-cirrhosis: (4.1% vs. 2.0% at 1 year, 6.3% vs. 3.1% at 2 years, 8.4% vs. 3.1% at 3 years, p = 0.015). The incidence was higher in patients with 2 or more positive tests compared to those with only 1 test (HR 4.0, 95%CI 1.1–13.9, p = 0.03). Among patients with no-cirrhosis (no positive test), age older than 65 (HR 5.2, 95%CI 1.6–17.4, p < 0.001) and post-treatment AFP>6.0 (HR 9.1, 95%CI 4.2–19.7, p < 0.001) was significantly associated with HCC development. HCC did not develop in 182 patients (25% of the cohort) who fulfilled the following criteria: no-cirrhosis (no positive test), age under 65, and post-treatment AFP <6.0.
Conclusion: The number of positive tests suggestive of cirrhosis, as defined by AASLD-IDSA simple algorism, correlated with the risk of HCC after SVR. Among no-cirrhosis patients, older age and post-treatment AFP>6.0 was associated with HCC risk. Addition of age and post-treatment AFP to simple blood criteria for no-cirrhosis could define the true no-HCC risk patients who may be discharged after SVR.

FRI441

Risk of end-stage renal disease among hepatitis C patients with chronic kidney disease treated with and without sofosbuvir

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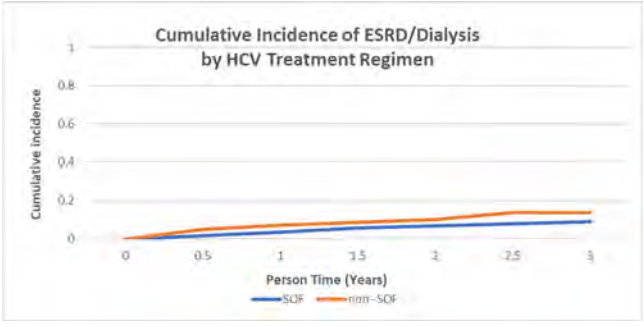
Background and Aims: Sofosbuvir (SOF) is a prodrug inhibitor of the hepatitis C virus (HCV) NS5B polymerase. The predominant circulating metabolite of SOF, GS-331007, is renally eliminated. Whether SOF affects kidney function is not well described. Using administrative claims data, we sought to characterize the risk of end-stage renal disease (ESRD) or dialysis among patients with chronic kidney disease (CKD) and HCV treated with SOF- and non-SOF-containing direct acting antiviral (DAA) regimens.
Method: 2,359 adult patients with evidence of interferon (IFN) -free DAA-treated HCV infection and claims indicating diagnosis of CKD were identified from a large US administrative claims database. All included patients had at least 1 year of continuous enrolment prior to cohort entry. Exclusion criteria were 1) prior claim for ESRD, dialysis, or kidney transplant, 2) simultaneous exposure to SOF and non-SOF DAA regimens, and 3) concomitant receipt of IFN. Patients were observed from initiation of the most recent DAA regimen to the first of: a claim for ESRD or dialysis, kidney transplant, discontinuation of insurance enrolment, or last date of data availability (September 2018). Absolute rates per 100 person-years (PYs) were calculated with exact 95% Poisson confidence intervals (CIs) at all stages of CKD combined and stratified for those patients with staging identified. Adjusted hazard ratios (HRs) estimating ESRD/dialysis risk associated with SOF- vs non-SOF-containing DAA regimens were calculated using Cox proportional hazards methods, after adjustment for baseline health status and treatment propensity score weighting.
Results: Overall, the unadjusted incidence of ESRD or dialysis was 3.88 (95% CI, 3.24–4.62) per 100 PY, with rates highest for patients with severe CKD (18.26; 95% CI, 12.79–25.28 per 100 PY). For the 1,976 SOF and 383 non-SOF DAA regimens, the unadjusted rates of ESRD or dialysis were 3.53 (95% CI: 2.89–4.28) and 7.41 (95% CI: 4.65–11.22) per 100 PY respectively. After covariate adjustment and treatment propensity score weighting, there was no significant difference in risk of ESRD or dialysis with vs. without SOF (adjusted HR = 0.77, 95% CI: 0.43–1.36). Similar results were observed when stratified by CKD stage.



Conclusion: The results of this analysis of real world data indicate no difference in risk of ESRD or dialysis in HCV-infected CKD patients treated with SOF- vs. non-SOF-containing DAA regimens.

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The weight of pre-existing cofactors for liver disease progression in patients who successfully eradicated chronic hepatitis C viral infection: an interim analysis in the PITER cohort

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Background and Aims: EASL clinical practice guidelines suggest that HCV patients who achieve an SVR need to be maintained on follow-up if pre-existing cofactors (CF) for liver disease progression such as excessive alcohol drinking, obesity and/or type 2 diabetes are present. In the PITER cohort, we evaluated the real life management of patients following HCV eradication according to liver disease stage and presence of these CF.
Method: Data of 4038 patients enrolled in PITER, who eradicated HCV were evaluated. Fibrosis stage was defined by elastometry and/or clinical evaluation for patients with cirrhosis.
Results: Of 1557 patients (mean age 57; SD: 13 years) with F1-F2 fibrosis stage, 77% had CF for liver disease progression. Of overall patients with F1-F2 stage, 30% had a follow-up (median 27 range: 19–34 months) after the SVR12. The prevalence of cofactors was 71% in those who continued follow-up versus 76% in those who interrupted it (p = 0.05). ALT remained elevated during the follow-up in 2% of patients with F1-F2 and CF compared to none of patient without. Of 473 patients (mean age 61;SD: 12 years) with F3 stage and a follow up (median 23; range 13–35 months) after the SVR, 89% had CF for disease progression. During the follow up, transaminase levels remained altered in 4% of patients with CF compared to none in those without CF (p = 0.02). In 3 (0.6%) patients with CF and F3 fibrosis stage at SVR, HCC was developed during the follow-up. Regarding the 2008 patients with cirrhosis, they were followed up for a median period of 33: range 26–41 months, the overall HCC incidence was 4.4% in those with CF and 3.9% in those without (p = 0.7). Factors independently associated to HCC occurrence were age (HR = 1.08; 95% CI 1.04–1.12), decreased albumin value (HR = 3.03 95% CI = 1.46–6.30) and genotype 3 (HR = 2.67 95% CI = 1.03–6.96). During the follow up, 3.2% of patients with decompensated cirrhosis, prior to antiviral treatment, had a new episode of decompensation whereas in 4.8% an incident decompensation episode was registered. Decompensation and worsening of Child Pugh class (found in 33%) were not associated with presence of CF for liver disease progression. Liver decompensation prior to treatment (HR = 7.13; 95% CI 4.51–11.27), platelets count lower than 100,000 (HR = 2.01; 95% CI 1.29–3.12) and decreased albumin values (HR = 1.65; 95% CI 1.08–2.54) were independently associated to liver decompensation.
Conclusion: The presence of cofactors for liver disease progression is common in patients with HCV who received antiviral therapy in Italy. Most physicians did not follow EASL recommendations and interrupted follow-up in F0-F2 patients regardless of the presence of CF. CF are associated with persistent post SVR ALT elevations in F0-F3 patients, but were not associated with higher incidence of HCC or liver related complications during a medium term follow up after HCV viral eradication.

FRI443
Clinical impact of direct-acting antiviral treatment on patients affected by hepatitis C virus-related oral lichen planus

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Background and Aims: Oral lichen planus (OLP) is a chronic inflammatory mucocutaneous disease, and it has been related to the hepatitis C virus (HCV) infection as one of the extrahepatic pathological manifestations. The current treatment for HCV infection with direct-acting antivirals (DAAs) is highly effective and safe. This study aimed to evaluate the impact of HCV eradication on OLP clinical manifestations.
Method: Patients (pts) with clinical and/or histological diagnosis of OLP and HCV chronic infection were recruited from the Oral Medicine and Internal Medicine Units of the University of Campania "Luigi Vanvitelli". All pts received DAAs treatment and were monitored at baseline, during, and after treatment for liver function and antiviral response. Patients received an oral clinical examination before DAAs (T0), 8 weeks after the end of treatment (T1) and were periodically followed. Statistical analysis was performed using Mann–Whitney and Wilcoxon tests, Chi-square, and Fisher's tests.
Results: Eighteen pts. (13 females and 5 males; median age years 75, range 44–87) with chronic HCV infection (10 pts. with 1b genotype; 7 pts with 2a/2c; 1 pt. with 3a) were enrolled. Fourteen pts. had chronic hepatitis and 4 liver cirrhosis. All pts. received DAAs as reported in Table 1. All pts. cleared HCV RNA and presented a sustained virologic response (SVR) at the follow-up (FU). No adverse events were reported. The median FU was 92 weeks at T2. At T0, five pts presented reticular and bilateral white lesions, 7 pts presented erosive OLP, and 6 presented a mixed form. The mean percentage of oral sites involved at T0 was 30% (±13.9), 20.8% (±12.9) at T1, and 16.2% (±15.2) at T2 showing a progressive improvement from T0 to T1 (p = 0.007) and T2 (p = 0.005). One patient developed oral cancer during the treatment and was excluded. Oral lesions have improved in 9 cases (52.9%) at T1 and in 10 cases (55.6%) at FU (T2); among these, 6 (60%) showed complete remission. However, statistical analysis did not reveal a significant correlation between oral improvement and HCV genotype (p = 0.64), viral load (p = 0.27), liver status (p = 0.60), isolated HBcAb positivity (p = 0.633) and type of DAA treatment received (p = 0.103).
Conclusion: DAAs treatment leading to HCV eradication can improve OLP symptoms. However, a causative relationship between HCV infection and OLP pathogenesis is difficult to establish. Further and larger studies are necessary.

FRI444
Identification of circulating microRNAs predictive of HCC in DAA-cured HCV-related cirrhosis

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Backround and aims: Treatment of patients with chronic hepatitis C (CHC) with Interferon (IFN)-based or DAA regimens leads to persistent viral eradication, i.e. sustained virological response (SVR). In CHC cirrhotic patient a successful antiviral therapy has been associated with the prevention of clinical decompensation and a strong reduction, but not the complete elimination, of the risk of developing HCC. The identification of those patients at higher risk of

Patient No.	Gender	Age	Liver disease	HCV genotype	Previous IFN treatment	DAAs treatment	Systemic disease except the liver disease	Smokers	Type of OLP before DAAs	Sites of OLP before DAAs (%)	Topical steroids to OLP before DAAs	Sites of OLP after DAAs - T1 (%)	Turning point of OLP after DAAs - T2 (%)	Topical steroids to OLP after DAA s
1	F	78	Cirrhosis	2a/2c		Sofosbuvir + Ribavirin	Kidney disease, Hypertension		Erosive OLP	40,0%	Yes	30%	20%	
2	F	80	Chronic Hepatitis	2a/2c		Sofosbuvir + Velpatasvir	Hypertension		Mixed OLP	60,0%	Yes	20%	20%	Yes
3	F	78	Chronic Hepatitis	1b	Yes	Ombitasvir/ Paritaprevir/ Ritonavir + Dasabuvir	Kidney disease, Hypertension, Diabetes	Ex smoker	Erosive OLP	35,0%	Yes	35%	35%	Yes
4	F	75	Chronic Hepatitis	1b		Sofosbuvir + Ledipasvir	Diabetes, Hypertension		Erosive OLP	20,0%	Yes	20%	Disappearance	
5	F	75	Cirrhosis	1b		Sofosbuvir + Ledipasvir			Mixed OLP	20,0%		10%	Disappearance	
6	M	70	Cirrhosis	1b		Sofosbuvir + Ledipasvir	Hypertension		Erosive OLP	40,0%	Yes	40%	40%	Yes
7	M	87	Chronic Hepatitis	1b		Elbasvir + Grazoprevir	Kidney disease, Hypertension		Reticular OLP	10,0%		5%	Disappearance	
8	F	68	Chronic Hepatitis	2a/2c		Glecaprevir + Pibrentasvir	Diabetes, Hypertension		Mixed OLP	45,0%	Yes	45%	45%	Yes
9	F	85	Chronic Hepatitis	2a/2c		Sofosbuvir + Velpatasvir	Hypertension		Mixed OLP	25,0%	Yes	25%	25%	Yes
10	M	72	Chronic Hepatitis	1b		Glecaprevir + Pibrentasvir			Reticular OLP	20,0%		20%	20%	Yes
11	F	74	Chronic Hepatitis	1b	Yes	Elbasvir + Grazoprevir	Diabetes, Hypertension		Mixed OLP	Excluded - Developed Oral Squamous Cells Carcinoma of the tongue				
12	F	62	Cirrhosis	2a/2c	Yes	Sofosbuvir + Ribavirin	Hypertension		Erosive OLP	25,0%	Yes	Disappearance	Disappearance	
13	F	73	Chronic Hepatitis	1b	Yes	Sofosbuvir + Velpatasvir			Mixed OLP	45,0%	Yes	25%	Disappearance	
14	M	44	Chronic Hepatitis	3a		Sofosbuvir + Velpatasvir	Hypertension	Smoker	Reticular OLP	10,0%		Disappearance	Disappearance	
15	F	78	Chronic Hepatitis	1b		Sofosbuvir + Ledipasvir	Diabetes, Hypertension	Smoker	Reticular OLP	25,0%		25%	25%	Yes
16	F	75	Chronic Hepatitis	1b		Elbasvir + Grazoprevir	Kidney Disease		Erosive OLP	20,0%	Yes	10%	10%	Yes
17	M	81	Chronic Hepatitis	2a/2c		Glecaprevir + Pibrentasvir			Reticular OLP	25,0%		25%	25%	Yes
18	F	59	Chronic Hepatitis	1b	Yes	Sofosbuvir + Ledipasvir		Ex smoker	Erosive OLP	45,0%	Yes	20%	10%	Yes

Figure: (abstract: FRI443)

developing HCC among HCV-related cirrhosis patients reaching an SVR represents an important unmet clinical need.

Methods: We performed a retrospective analysis of circulating miRNAs using the NanoString nCounter® technology in selected patients from a prospective longitudinal cohort of 565 HCV cirrhotic patients treated with DAAs in a single clinical center. The study population comprised 12 cirrhotic patients treated with DAA reaching SVR who developed HCC (sera collected before starting DAA treatment (*HCV pre-DAA HCC*) and at HCC diagnosis (*HCV SVR HCC*)) and a case-control cohort of 12 DAA-treated patients who did not develop HCC over a comparable follow-up period after SVR (sera collected before starting DAA treatment (*HCV pre-DAA*) and at SVR (*HCV SVR*)).

Results: Principal component analysis of >800 circulating miRNA profiles from the 4 groups showed that DAA-treated patients who develop an HCC after SVR (*HCV SVR HCC*) cluster tightly together and are well separated from the DAA-treated patients who do not develop an HCC after SVR (*HCV SVR*). Unsupervised hierarchical clustering analysis shows that HCV eradication has a strong impact on circulating miRNAs and that HCC development is accompanied by a further reduction of the number of circulating miRNAs detected, supporting the notion that the profile of circulating miRNAs in the HCV SVR HCC patients is the result of both HCV eradication and HCC development. Four miRNAs were specifically detected in the *HCV pre-DAA HCC* patients who will develop HCC after DAAs treatment and SVR but not in the *HCV pre-DAA* patients who do not develop HCC.

Conclusion: Circulating miRNAs identifies miRNAs that are associated with a higher risk of developing HCC after DAA treatment and HCV eradication in patients with HCV-related cirrhosis. These miRNAs are canditates to be included in new clinical/biological scores to predict HCC in relevant populations of HCV-infected patients.

FRI445

Impact on health perception, quality of life and labor productivity of antiviral treatment for hepatitis C in patients without significant fibrosis

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Background and Aims: Among the extrahepatic manifestations of chronic hepatitis C virus (HCV) infection, asthenia is estimated at up to 61% of those affected. Improvement in Patient Recorded Outcomes (PROs) related to quality of life has been described with obtaining a sustained viral response (SVR12) after the use of direct-acting antivirals (DAA) in registration studies, but to a lesser extent in real life, and on samples that also included patients with variable degrees of fibrosis. In our study, we treated to assess the effect of DAA treatment in patients with chronic HCV infection with low fibrosis

(F0-F1) on asthenia, perception of quality of life and work productivity.
Method: Multicenter prospective longitudinal case series, between May 2018 and April 2019. Monoinfected patients with low fibrosis (Elastography <7.1 kPa or Fib-4 <1.45) filled in FACIT-F validated questionnaires (assess asthenia and physical, social, emotional well-being and functional) and WPAI for hepatitis C (assesses absenteeism, presenteeism and deterioration in work and daily performance), prior to therapy and in visit of SVR12.
Results: 156 patients were included, 118 of whom completed the forms in both visits, in 5 hospitals. Only 1 did not obtain SVR12. Significant improvement was obtained in the FACIT-F scoring in SVR12 with respect to the baseline both globally and in each of the sub-spheres (Fig 1, up). In the analysis of the possible associated variables, an increase in the overall score ≥ 10% (obtained by 59 patients, 50.4%), only full-time employment was related to such improvement (54.2% vs. 43.4%, p = 0.033). In the figure (bottom), we show the variables associated with greater positive or negative changes in FACIT-F global score, analyzed by mixed effects model. In the WPAI questionnaire, there was no significant improvement in percentage of absenteeism, presenteeism, or performance deterioration in the employed patients, but a lower deterioration of non-work performance attributed to HCV, in the total sample (from 21% to 14%, p = 0.013).
Conclusion: The successful treatment of HCV with AA in patients with minimal or absent liver fibrosis results in an improvement in the physical, social, emotional and functional well-being of the subject, as well as in their subjective level of fatigue, especially in patients who work full time. In addition, it improves the performance capacity of daily activities, although it does not modify the indexes of labor productivity.

FRI446

Sustained virologic response to direct-acting antivirals does affect the risk of portal vein thrombosis in patients with advanced chronic liver disease

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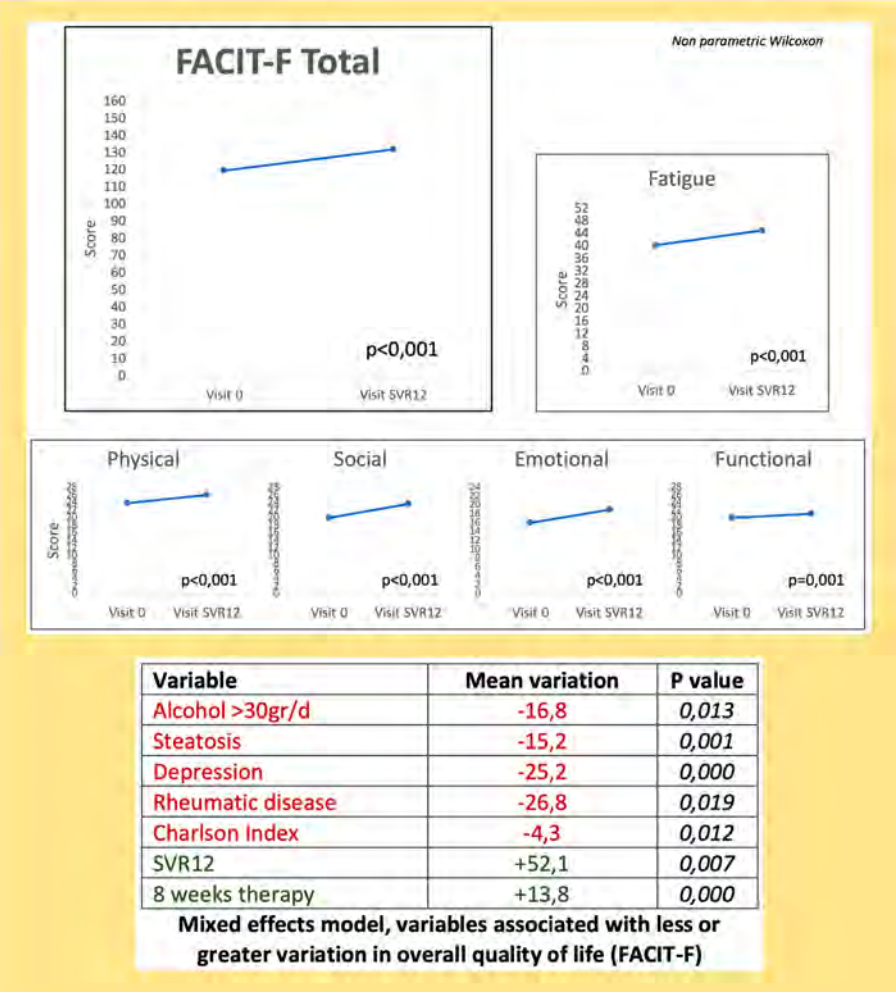
Background and Aims: Sustained virologic response (SVR) to direct-acting antivirals (DAA) ameliorates portal hypertension and improves hepatic function in HCV-related advanced chronic liver disease (ACLD). Studies performing thrombomodulin-modified thrombin generation assays reported no change or even a regression of the

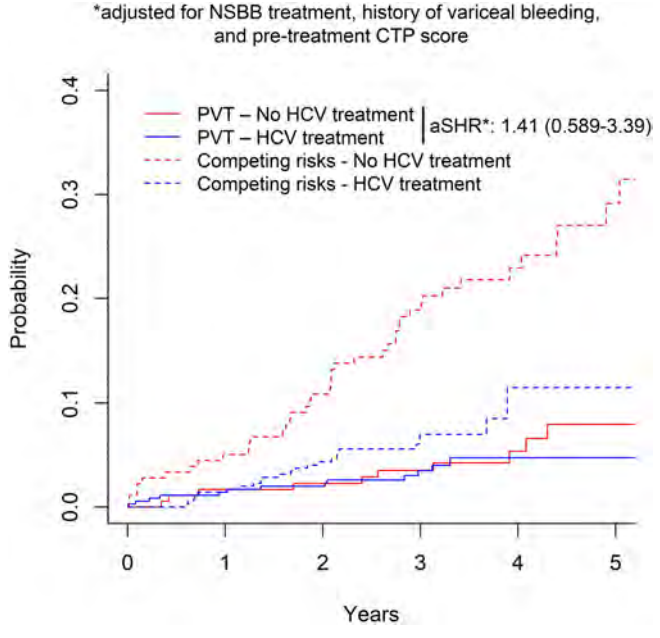


Variable	Mean variation	P value
Alcohol >30gr/d	-16,8	0,013
Steatosis	-15,2	0,001
Depression	-25,2	0,000
Rheumatic disease	-26,8	0,019
Charlson Index	-4,3	0,012
SVR12	+52,1	0,007
8 weeks therapy	+13,8	0,000

Mixed effects model, variables associated with less or greater variation in overall quality of life (FACIT-F)

Figure: (abstract: FRI445)

in vitro hypercoagulability that was observed pre-treatment. However, a worrisome incidence of portal vein thrombosis (PVT) immediately after antiviral therapy has recently been reported.
Therefore, we aimed to analyze the long-term impact of SVR on the development of PVT based on two independent, large, well-characterized cohorts of patients with chronic hepatitis C (CHC) and ACLD.
Method: All patients underwent standardized ultrasound every 6 months; PVT was confirmed by cross-sectional imaging.
Patients entered the time-to-event analyses at end of antiviral therapy ('**HCV treatment**' cohort**;** n = 358) or at the time of inclusion in a prospective study ('**No HCV treatment**' cohort; n = 179). The event of interest in the main analysis was PVT, while events hindering its observation (i.e., tumoral PVT, liver transplantation, or death) or modifying the risk (i.e., transjugular intrahepatic portosystemic shunt (TIPS) or anticoagulation) were considered as competing risks. '**No HCV treatment**' patients were censored at the start of antiviral therapy.
Results: At treatment initiation ('**HCV treatment**')/study inclusion ('**No HCV treatment**'), 18% of patients were Child-Turcotte-Pugh (CTP) stage B/C and the median MELD was 8 (interquartile range: 8–11). Thirteen (3.6%) patients in the '**HCV treatment**' cohort developed a PVT during a median follow-up of 3.1 years, while 10 (5.6%) patients in the '**No HCV treatment**' cohort were diagnosed with PVT during a median follow-up of 3.5 years. High pre- (per point; adjusted subdistribution hazard ratio (aSHR): 1.32 (1.08–1.82)) and post-treatment (aSHR: 1.94 (1.03–3.66)) CTP scores were the only independent risk factors for PVT development. HCV cure did not modify the risk of PVT in competing risk regression models adjusted for previous variceal bleeding, use of non-selective beta-blockers, as well as severity of hepatic dysfunction pre- (SVR vs. non-SVR; aSHR: 1.41 (0.589–3.39); Figure) or post-treatment (aSHR: 1.44 (0.588–3.54)). However, SVR was associated with a substantial reduction of adverse outcomes (a composite of TIPS, liver transplantation, or death; e.g., aHR: 0.204 (0.1–0.418)) and mortality (e.g., aHR: 0.162 (0.06–0.44)).



Conclusion: Although HCV cure reduces the risk of adverse outcomes, and in particular, mortality, it does not affect the risk of PVT in patients who have pre-treatment ACLD. Accordingly, ACLD patients achieving SVR remain at risk for PVT, and thus, should be carefully monitored for PVT. The risk for PVT is increased in patients with impaired hepatic function pre- or post-treatment.

FRI447

The one-year outcome of hepatitis B virus in Taiwanese patients with chronic hepatitis B and C co-infection after direct-acting antivirals

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Background and Aims: The long-term outcome of hepatitis B virus (HBV) infection among patients dually infected with HBV and hepatitis C virus (HCV) receiving direct-acting antivirals (DAA) therapy remains unclear. We aimed to investigate thedynamicchange of hepatitis B surface antigen (HBsAg) and reactivation of HBV in the clinical setting.
Method: A total of 79 HBV/HCV dually-infected patients who completed DAA therapy with at least 3-month posttreatment follow-up were enrolled. HBsAg titer and HBV DNAwere measured before, during and post-DAA therapy. The primary endpoint was HBsAg seroclearance; secondary endpoints included changes of HBsAg titer, HBVreactivation (>1 log increase or >100 IU/ml in HBV DNA if baseline undetectable), and hepatitis flare.
Results: The HBsAg declined from a median of 73.3 IU/ml at baseline to 16.2 IU/ml at end-of-DAA and gradually increased to 94.1 IU/ml at 12 months post-DAA. During a mean follow-up period of 11.1 months (range, 3–36 months), eight (10.1%) of the 79 patients developed HBsAg seroclearance, including four during the DAA therapy. The cumulative probability was 10.3% at 12 months post-DAA. Pre-treatment HBsAg ≤10 IU/ml was the only factor associated with HBsAg loss (HR: 8.52, 95% CI: 1.048–69.312, p = 0.045). Thirty (38.0%) patients experienced an HBV reactivation with a 12-month cumulative probabilityof 40.4%. Pre-treatment HBsAg >10 IU/ml was the only factor associated with HBV reactivation (HR: 2.88, 95% CI: 1.057–7.844, p = 0.039). Six patients (2 non-cirrhotic, 4 cirrhotic) happened HBV related clinical reactivation; Three of the four cirrhotic patients developed liver failure with two mortality despite of immediate anti-HBV nucleos(t)ide therapy.
Conclusion: HBsAg loss could develop among HBV/HCV dually infected patients receiving DAA therapy, especially those with low pre-treatment HBsAg titer. Prophylactic anti-HBV therapy is mandatory for patients with baseline cirrhosis, irrespective of HBV DNA levels.

FRI448

Hepatitis C reinfection by treatment pathway among people who inject drugs in Tayside, Scotland

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Background and Aims: The efficacy of pan-genotypic direct acting antivirals (DAA) provide an excellent opportunity to scale up Hepatitis C (HCV) diagnosis and treatment, ultimately achieving the WHO target of HCV elimination by 2030. However, HCV reinfection among people who inject drugs (PWID) remains a concern and may impede elimination efforts. We assessed reinfection rates among people with a risk factor for HCV of intravenous drug use, including

PWID, and those on opiate substitution therapy (OST), across six specialised treatment pathways in Tayside, Scotland.
Method: Data was collected retrospectively for every treatment episode that resulted in a sustained viral response (SVR) after undergoing treatment. Reinfection rates were calculated for each treatment pathway: hospital outpatient clinic; community pharmacy; drug treatment outreach; prison clinic; nurse led outreach clinic; and injection equipment provision site. Reinfection is defined as a positive RNA test result after SVR. Incidences of reinfection are expressed in 100 person-years (PYs).
Results: In total, 1175 treatment episodes were identified that resulted in a SVR after treatment. Of these, 100 reinfections were identified, generating an overall reinfection rate of 5.3 per 100 PYs (95%CI: 4.4–6.4). Reinfection rates per treatment pathway are displayed in Table 1. The hospital outpatient clinic had the lowest reinfection incidence of the six treatment pathways (1.8 per 100 PYs, 95%CI: 1.1–2.9), with the injection equipment provision site treatment pathway having the highest reinfection incidence (19.9 per 100 PYs, 95%CI: 14.9–26.5).

Treatment Pathway	Reinfection rate per 100 PYs (95%CI)
Hospital outpatient clinic	1.8 (1.1–2.9)
Drug treatment outreach	3.1 (1.6–6.2)
Nurse led outreach	6.4 (4.0–10.1)
Prison clinic	8.1 (4.9–13.5)
Community pharmacy	12.1 (6.3–23.2)
Injection equipment provision site	19.9 (14.9–26.5)

Conclusion: Specialised treatment pathways in Tayside yield varying reinfection incidence rates. Our results suggest that resources should be targeted at the injection equipment provision site treatment pathway in order to reduce the incidence of reinfection and achieve elimination targets. It is imperative that harm reduction services are available and regular post treatment HCV testing is carried out in order to reduce reinfection risk among PWID.

FRI450

Influence of DAA treatment in patients with HCV-cirrhosis and esophageal varices on liver transplant free survival and risk of developing hepatocellular carcinoma

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Background and Aims: Most evidence on the benefit of DAA treatment is based on series with SVR. The presence of esophageal varices (EV) is associated with a higher probability of presenting complications of cirrhosis and hepatocellular carcinoma (HCC). To know the influence of DAA treatment in HCV-cirrhosis (CC) with EV on transplant-free survival (TFS) and risk of HCC.
Method: All patients with CC, viremic, Child A/B, with EV prospectively followed bianually in a HCC surveillance programme (n = 383) were analyzed. 146 (38%) received DAA (DAAp); the start of treatment was the time of inclusion. Follow-up was censored at month 54. 16 variables collected at inclusion were analyzed.
Results: Male 70%, age 55 years, 33% with previous decompensation (PD), 81% Child A. DAAp were older (55 vs 53; p = 0.012) and obtained SVR more frequently (95% vs 4%; p < 0.001), without differences in the rest of the variables. During 42 months of follow-up (27–54), 104 (27%) received a liver transplant (LT)(n = 33) or died (n = 71) (TFS at 54 months: 68%). In the univariate analysis, PD (p < 0.001), alcohol consumption (p = 0.001), ALT>ULN (p = 0.024), platelets $<100 \times 10^3/mm^3$, Child B (p < 0.001), no1-GT (p = 0.006), BMI 25–30 (p = 0.019), inclusion prior to 2005 (p < 0.001) and not having received DAA (no-DAAp)(p = 0.001) were associated with lower TFS. TFS at 54 months was 61.5% in no-DAAp and 80% in DAAp. In the multivariate analysis, no1-GT (HR:1,724; 95% CI:1,082–2,749), PD (HR:2,812; 95% CI:1,737–4,551) and CHILD B (HR:2,156; 95% CI:1,307–2,749) were associated with a higher risk of death/LT, while DAAp had lower risk (HR:0.463; 95% CI:0.283–0.760). During a follow-up of 39 months (21–54), 56 (15%) developed HCC. Age>53 years (p = 0.007), HBsAg (p = 0.014), PD (p = 0.007), platelets $<100 \times 10^3/mm^3$ (p = 0.016) and Child B (p = 0.003) were associated with an increased risk of HCC at the univariate analysis. The probability of developing HCC at 54 months was 21% in no-DAAp and 13.4% in DAAp (p = 0.16). In multivariate analysis, age>53 (HR:2,407; 95% CI:1,334–4,340), HBsAg (HR 4,970; 95% CI:1,540–16,042), platelets $<100 \times 10^3/mm^3$ (HR: 1,858; 95% CI: 1,009–3,422; p = 0.047) and Child B (HR:2,539; 95% CI: 1,397–4,616) were associated with increased risk of HCC, while no association was observed with DAA (HR:0.614; 95% CI: 0.312–1.210).
Conclusion: DAA treatment, regardless of SVR, increases transplant-free survival in Child A/B HCV-cirrhotic patients with EV, without increasing the risk of developing HCC.

FRI451

Dynamic changes of serum M2BPGi as a fibrosis marker of patients with HCV mono-infection and HCV/HIV co-infection receiving direct-acting anti-viral therapy

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Background and Aims: Significant fibrosis regression has been observed in patients with chronic hepatitis C virus (HCV) infection after direct-acting anti-viral (DAA) therapy, particularly individuals with sustained virological response (SVR). The aim of this study was to evaluate dynamic changes of serum Mac-2 binding protein glycosylation isomer (M2BPGi) levels in patients with HCV genotype 1, who received elbasvir/grazoprevir (EBR/GZR) therapy.
Method: A total of 85 patients, who received EBR/GZR with or without ribavirin for 12 or 16 weeks in a clinical trial were included. Serum M2BPGi were serially measured by an automated lectin-antibody sandwich immunoassay at baseline, during and after therapy. Using magnetic resonance elastography (MRE) as a reference, the diagnostic performance of serum M2BPGi at baseline and SVR24 were compared to those of transient elastography (TE) and AST/platelet ratio index (APRI).
Results: Overall 59 HCV mono-infected and 26 HCV/HIV co-infected patients were analyzed. SVR24 rates in the mono- and co-infected groups were 93.2% and 96.2%, respectively. The correlations with MRE at baseline for TE, M2BPGi and APRI were r = 0.788, r = 0.703 and r = 0.564, respectively (all P < 0.001). Based on MRE, the area under the ROC curves for TE, M2BPGi and APRI in differentiating significant fibrosis (≥F2) were 0.89 (95%CI; 0.82–0.96, P < 0.001), 0.84 (0.76–0.93, P < 0.001) and 0.76 (0.66–0.87, P < 0.001), respectively. The corresponding figures for distinguishing severe fibrosis (≥F3) were 0.93 (0.88–0.99, P < 0.001), 0.92 (0.86–0.98, P < 0.001) and 0.81 (0.71–0.92, P < 0.001), respectively. Overall, all fibrosis markers were significantly changed at the time of SVR24 compared with their baseline levels. The correlations with MRE at SVR24 for TE, M2BPGi and APRI were r = 0.63(P < 0.001), r = 0.503(P < 0.001) and r = 0.359(P = 0.001), respectively. Of note, serum M2BPGi levels gradually declined during and after therapy in only patients achieving SVR24 (responders) but not in patients without SVR (non-responders). In responders, M2BPGi reduction from baseline were 0.8 ± 1.0 COI at week 4, 1.0 ± 1.3 COI at end-of-therapy, 1.4 ± 1.5 COI at SVR12 and 1.4 ± 1.5 COI at SVR24 (all P < 0.001). The corresponding figures for non-responders were 0.3 ± 0.5, 0.4 ± 0.6, 0.4 ± 0.3 and 0.1 ± 0.3 COI,

respectively (all P > 0.05). In multivariate analysis, age, the presence of significant fibrosis at baseline and achieving SVR24 were independent factors associated with M2BPGi reduction.
Conclusion: Compared to APRI, serum M2BPGi represented a better non-invasive marker for the assessment of liver fibrosis at baseline and after DAA therapy in patients with chronic HCV infection. Serum M2BPGi significantly declined during the administration of DAA, particularly in patients achieving SVR24. Moreover, the dynamic changes of serum M2BPGi were not influenced by the status of HIV co-infection.

FRI452
Non-invasive tests of fibrosis and risk of liver-related complications: observations following successful sofosbuvir-based treatment in patients with HCV cirrhosis

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Background and Aims: Noninvasive tests of fibrosis (NITs) are an alternative to liver biopsy for fibrosis staging and monitoring; however, associations between NITs and disease progression are poorly understood. Our aim was to evaluate the risk of liver-related complications according to baseline at enrolment (BL) and changes in the Enhanced Liver Fibrosis (ELF) test and liver stiffness by transient elastography (LS by TE) following sustained virologic response (SVR) in patients with HCV cirrhosis.
Method: Patients with pre-treatment HCV cirrhosis who achieved SVR with sofosbuvir (SOF)-based regimens were enrolled in an ongoing, prospective registry (NCT02292706). Patients underwent routine clinical and laboratory assessments, including semi-annual ELF testing and annual LS by TE. At BL, fibrosis stage was defined based on ELF (F0-F2, <9.8; F3, 9.8–11.3; F4, >11.3) and LS by TE (F0-F2, <9.6 kPa; F3, 9.6–12.5 kPa; F4, >12.5 kPa). Changes at 48 weeks (improved, no change, worse) were defined based on ELF response (≥0.5 unit change from BL) and LS by TE response (≥25% change from BL). Associations between NITs and all-cause mortality, hepatocellular carcinoma (HCC), and total liver-related events (hepatic decompensation, transplantation, HCC, and liver-related death) were evaluated using Cox regression.
Results: We included 1,370 subjects with HCV Child-Pugh A cirrhosis (median 60 years of age, 32% female). At BL, median ELF was 9.8 (IQR 9.1, 10.7); 530 (39%) and 158 (12%) patients had ELF scores consistent with F3 and F4 fibrosis, respectively. Median LS by TE was 13.9 kPa (IQR 9.1, 21.3); 210 (15%) and 640 (47%) patients had LS by TE consistent with F3 and F4 fibrosis, respectively. After a median follow-up from BL of 144 weeks (IQR 119, 172), BL ELF and LS by TE class were associated with risks of all-cause mortality, HCC, and liver-related events (Table). Relative to BL F0-F2, significantly increased risks for all outcomes were observed for both F3 and F4 fibrosis defined by ELF, and F4 fibrosis defined by LS by TE. Worsening of ELF at 48 weeks was significantly associated with increased risk of all-cause mortality, while risks of HCC and total liver-related events were numerically, but non-significantly, higher for this group. In contrast, worsening of LS by TE at 48 weeks was not significantly associated with increased risks of the studied outcomes. Improvements in either measure were not associated with the risk of complications.
Conclusion: Following successful HCV therapy in patients with HCV-related cirrhosis, BL NITs are prognostic. Changes in NITs over 48 weeks may also be predictive of disease progression; however, further study is necessary following the accrual of additional follow-up time and events. This study is among the first to show an association between changes in liver fibrosis and changes in liver-associated morbidity and mortality in patients with compensated cirrhosis.

FRI453
Hepatocellular carcinoma following direct acting antiviral therapy does not display an aggressive pattern: a prospective study

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Background and Aims: Chronic hepatitis C (CHC) remains the most common cause of hepatocellular carcinoma (HCC). Currently, there is an accumulating evidence demonstrating a benefit of direct-acting antiviral (DAA) therapy in reducing incident HCC among HCV-

Table: Associations between NITs at baseline and their change with liver-related complications.

	All-Cause Mortality				HCC				Total Liver-Related Events			
	N pats	N events	HR (95% CI)	p-value	N pats	N events	HR (95% CI)	p-value	N pats	N evets	HR (95% CI)	p-value
Baseline ELF Class*												
<9.8	673	6	1.0 (ref)	-	668	19	1.0 (ref)	-	656	48	1.0 (ref)	-
9.8-11.3	530	13	2.8 (1.1-7.4)	0.0380	525	31	2.1 (1.2-3.7)	0.0142	462	65	2.0 (1.4-2.9)	0.0004
>11.3	158	16	12.0 (4.6-31.3)	<0.0001	155	19	4.3 (2.2-8.2)	<0.0001	120	38	4.9 (3.2-7.6)	<0.0001
Baseline LS class*												
<9.5	320	2	1.0 (ref)	-	318	9	1.0 (ref)	-	317	19	1.0 (ref)	-
9.6-12.5	210	2	1.4 (0.2-9.9)	0.7433	208	10	1.6 (0.6-3.9)	0.3097	204	14	1.1 (0.5-2.2)	0.8087
>12.5	640	20	5.1 (1.2-21.7)	0.0290	631	41	2.3 (1.1-4. 8)	0.0222	547	99	3.2 (2.0-5.2)	<0.0001
ELF Change W48**												
Improved	223	5	1.0 (0.3-2.7)	0.9458	217	7	0.7 (0.3-1.7)	0.4493	189	13	0.8 (0.5-1.6)	0.6021
No change	751	13	1.0 (ref)	-	732	28	1.0 (ref)	-	653	45	1.0 (ref)	-
Worse	224	12	4.5 (2.0-9.9)	0.0002	216	9	1.4 (0.7-3.0)	0.3871	188	16	1.5 (0.9-2.7)	0.1516
LS Change W48**												
Improved	271	6	1.2 (0.4-3.6)	0.6977	265	10	0.8 (0.4-1.6)	0.4844	242	18	0.8 (4.7-1.5)	0.5353
No change	538	8	1.0 (ref)	-	527	23	1.0 (ref)	-	466	34	1.0 (ref)	-
Worse	162	4	1.7 (0.5-5.7)	0.4133	156	5	0.8 (0.3-2.1)	0.6219	136	12	1.3 (0.7-2.6)	0.4221

* Adjusted for age and gender ** Adjusted for age, gender, and baseline value

Figure: (abstract: FRI452)

infected patients, however the changes in HCC incidence over time following HCV eradication and impact of these therapies on tumor behavior is less clear. Here, we identified incident HCC after HCV eradication and compared the characteristics of HCC diagnosed before starting of DAA therapy with those of de novo HCC which developed following DAAs treatment in large population based cohort.

Method: In an outreached program in 73 villages across Egypt, 204,749 individuals were screened for HCV antibody and HBsAg, 15,892 (7.8%) were viremic of those 14,495 (91.2%) were treated with DAAs. Liver fibrosis was assessed by FibroScan and 1671 patients and 616 were showed to have cirrhosis (F4) and advanced fibrosis (F3), respectively. Of those, 166 patients had active HCC before initiation of DAA therapy (group I). Patients were followed after treatment for median of two years (12–45 months), during which 109 incident HCCs were identified (group II).

Results: 11 out of the 109 de novo HCC cases (10.1%) occurred during the first year of follow up, 53 (48.6%) during the second year, 35 (32.1%) during the third years, while 10 (9.2%) occurred after the third year of follow up. Notably, according to BCLC classification; advanced stages (BCLC-C and D) were significantly lower group II than group I (26.6% & 3.7% vs 36.1% &8.4% respectively, $p < 0.001$). BCLC stage B is significantly higher in Group II (30.3% vs 16.3%, $p < 0.001$). Portal vein invasion was also significantly lower in group II than group I (7.3% vs 44%, $p < 0.001$).

Conclusion: Patients with baseline cirrhosis or significant fibrosis maintain an increased risk for HCC up to 4 years after HCV eradication. However, HCC developed in those patients tend to display less aggressive pattern when compared to HCC diagnosed before DAAs therapy. Further studies are required to clarify the mechanisms of these effects and duration of ongoing HCC surveillance after HCV eradication.

FRI454

Long-term evaluation of liver stiffness in HCV patients after sustained virological response to DAAs: predictive factors for disease improvement and hepatocellular carcinoma development

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Background and Aims: The viral clearance by direct-acting antiviral agents (DAAs) in HCV setting is associated with an early liver stiffness (LS) reduction. However, in patients who obtain a sustained virological response (SVR), the long-term progression of LS remains still unclear. Aim of the study is thus the assessment of long-term changes in LS and any factors negatively affecting its decline.

Method: This is an observational multicenter study. All patients with chronic HCV infection treated by DAAs who achieved a SVR were enrolled from 6 italian Center. Clinical, laboratory and instrumental (ultrasound and transient elastography) evaluations were performed pre-treatment (T0), at 6 (T6) and 24 months (T24) since the end of therapy.

Results: 466 HCV patients, of which 276 with cirrhosis, were enrolled and evaluated for a mean follow-up time of 23 months. LS significantly decreased from T0 to T6 (median 14.3 kPa vs. 11.1 kPa, $p = 0.002$), with a progressive reduction till T24 (8.7 kPa, $p < 0.001$). Only patients with liver steatosis and HCC onset not showed a significant late LS improvement. Moreover, a ROC curve analysis on LS for the risk of HCC development showed that a LS pre-treatment cut-off of 21.4 kPa (sensitivity 70%, specificity 83%) (AUC:0.756, 95% C.I.

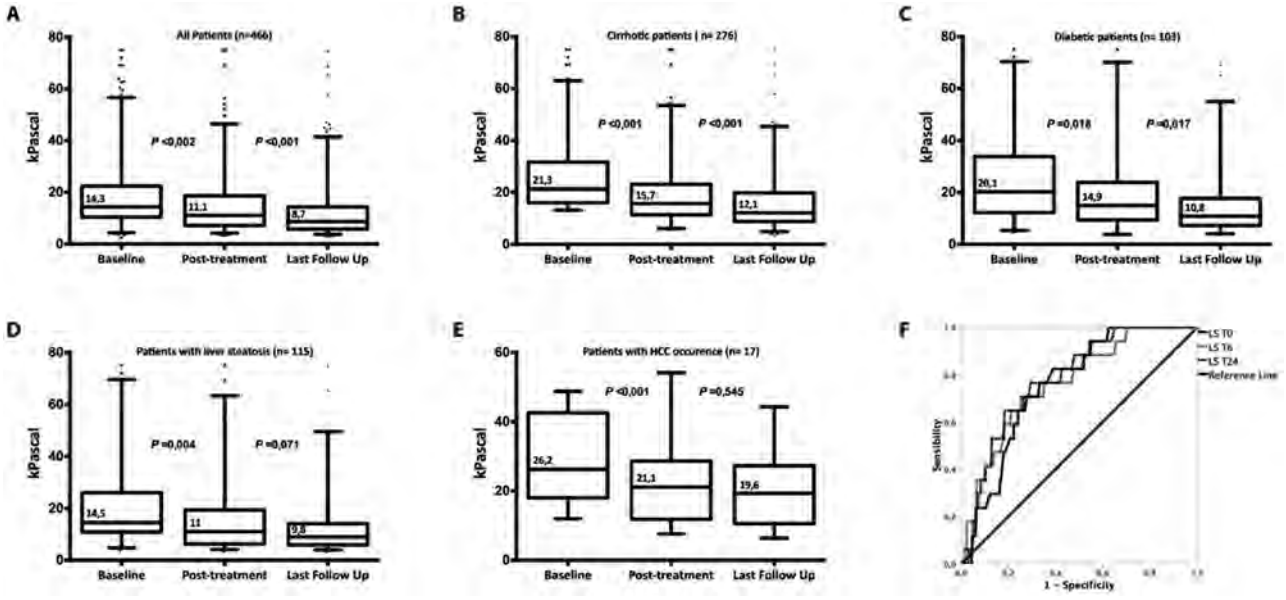

Figure 1: (abstract: FRI454): Box-plots: (a) LS changes over time in all patients; (b) in cirrhotic subgroup; (c) in diabetic patients; (d) in patients with liver steatosis and (e) in HCC patients. (f) ROC curve for HCC occurrence at the three LS time-points.

0.665–0.846; p < 0.001) and a LS post-treatment (T6) of 14.0 kPa (sensitivity 70%, specificity 86%, AUC:0.765, 95% C.I. 0.658–0.873; p < 0.001) were predictive for HCC onset. At univariate analysis, BMI, LS-pre-treatment >21.4 kPa and LS post-treatment >14.0 kPa were associated with a higher HCC development risk. However, at the multivariate only LS post-treatment (T6) >14.0 kPa was independently associated with an increased risk of HCC onset (O.R: 9.316, 95% C.I. 1.158–74.939; p = 0.036).

Conclusion: Our findings show that SVR achievement allows a progressive LS decline, even in the long-term. Hepatic steatosis and HCC development seem to negatively affect late LS changes. Moreover, a failure in long-term LS reduction could represent a potential risk factor for HCC onset. Patients showing a post-treatment LS >14 kPa seem to have a higher risk of HCC development. Therefore, this subset should undergo intensive surveillance protocols.

FRI455

Hepatitis C virus infection, endogenous retrotransposons activation and cancer risk

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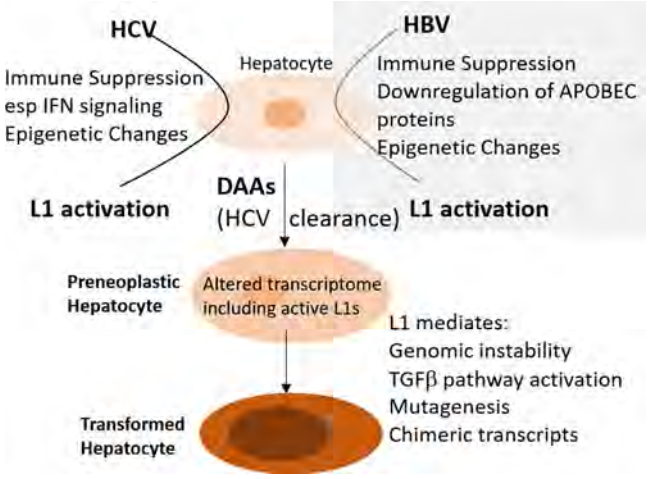
Background and Aims: Mortality from hepatocellular carcinoma (HCC) continues to rise, due to a combination of late detection and lack of curative treatments. Chronic Hepatitis C (CHC) virus infection is a major risk factor for HCC and the use of direct acting antivirals (DAAs), potentially curing HCV infection, heralded a major breakthrough. However, the risk of HCC persists even after HCV clearance. The key drivers of HCC in chronic liver disease remain elusive, as do the mechanisms post-DAAs. Recently, we demonstrated the activation and mutagenic consequences of long-interspersed repeat elements (L1 s) in human HCC, when the epigenetic silencing of these elements is compromised. Since HCV infection contributes to global epigenetic changes, we hypothesise that L1 s become activated during the process, mediating genomic instability, with chimeric transcripts and consequent upregulation of TGFβ signaling leading to cancer development post viral clearance. We aimed to evaluate activation of L1 s in chronic hepatitis C patients, in association with viral hepatitis-associated HCC development and prognosis.

Method: L1 transcript expression was evaluated in RNAseq datasets of CHC (GSE84346) and The Cancer Genome Atlas-Liver Hepatocellular Carcinoma (TCGA-LIHC) with an in-house pipeline. Immunohistochemical (IHC) examination of L1orf1 protein (L1orf1p) in the biopsy and/or resection tissue of CHC and CHC-HCC patients was using an automated Ventana system. An *in vitro* engineered-L1 retrotransposition assay in Huh7 cells in the presence or absence of an HCV replicon evaluated the influence of HCV on retrotransposition rate.

Results: Liver L1 transcripts were upregulated in GSE84346 CHC patients compared to controls (p = 0.001), as well as in TCGA-LIHC non-tumour tissue in patients with a history of viral hepatitis or alcohol abuse (p < 0.05). In our own IHC pilot study, the L1 status of HCC expression in diagnostic biopsies matched that of L1orf1p expression in the non-tumour biopsy tissues predating HCC development by a number of years. *In vitro*, there was a 4-fold increase in retrotransposition rate in Huh7-HCV compared to control Huh7 cells, confirming an influence of HCV on retrotransposons activation.



Model depicting activation of L1 upon HCV infection, contributing to HCC development.

Conclusion: L1 can be activated before oncogenic transformation in patients with chronic HCV infection, with HCV promoting retrotransposition and potentially its mutagenic consequences. Persistence of L1 activation may contribute to HCC development even beyond viral clearance.

FRI456

Post-treatment wisteria floribunda agglutinin-positive mac-2-binding protein is a useful predictor of hepatocellular carcinoma development after hepatitis C virus eradication

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Background and Aims: Interferon (IFN)-free therapy of hepatitis virus C (HCV) has higher efficacy than previous IFN-based therapy, and a large number of patients currently achieve a sustained virological response (SVR). Although the eradication of HCV reduces the incidence of hepatocellular carcinoma (HCC), HCC development is not rarely observed even in patients achieved SVR. Wisteria floribunda agglutinin-positive Mac-2-binding protein (WFA+-M2BP) was recently developed as a noninvasive glycolbiomaker of liver fibrosis. Previously, we reported that pre-treatment serum WFA+-M2BP level is a useful predictor for HCC development after SVR by IFN-based therapy. However, it remains unclear the change of WFA+-M2BP level after viral eradication and its association with HCC development.

Method: A total of 522 patients achieved SVR (IFN-based therapy, 228; IFN-free therapy, 294) were included. Patients with follow-up period of<0.5 year after the end of treatment (EOT) were excluded. Serum WFA+-M2BP levels were measured before treatment and at 24 weeks after EOT. Univariate and multivariate Cox proportional hazard analysis were used to estimate the hazard ratios (HRs) for HCC development and, Kaplan-Meier method and log-rank test were used to determine the cumulative incidence of HCC development.

Results: During the median follow-up time of 2.9 years, 14 patients developed HCC. The estimated cumulative incidences of HCC development in the entire cohort were 1.7% and 3.3% at three and five years, respectively. WFA+-M2BP levels were significantly reduced after SVR (P < 0.001). Multivariate analysis revealed that high WFA +-M2BP level at SVR24 (HR = 1.215, p = 0.020), low platelet counts at pre-treatment (HR = 0.876, p = 0.036) and elderly patients (HR = 1.073, p = 0.011) were independent risk factors for HCC development. From the receiver operator characteristics curve analysis, WFA +-M2BP level >1.37 COI was identified as a cut-off value with an adjusted HR 12.2 (95%CI 3.41–43.91, p < 0.001). The three- and five-year cumulative incidence of HCC in patients with low WFA+-M2BP at

SVR24 were 0.7% and 0.7%, respectively, whereas those of patients with high WFA+-M2BP were 4.8% and 12.4%, respectively (p < 0.001). In addition, WFA+-M2BP was significantly associated with HCC development stratified by IFN-based and IFN-free therapy.
Conclusion: Post-treatment WFA+-M2BP is a useful predictor for HCC development after achievement of SVR, possibly even in IFN-free therapy era.

FRI457
Erradication of HCV with direct-acting antivirals increased small LDL particle number in SVR48

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Background and Aims: HCV interferes with the lipid metabolism of the host, producing low levels of VLDL and LDL-cholesterol. Its eradication with direct-acting antivirals (DAA) causes an increase in LDL-cholesterol. It is still not clear whether those changes might alter the atherogenic risk of individuals treated with DAA. To analyze the lipid profile associated with HCV infection and its variation after DAA eradication and at the SVR48, using the 2D DOSY NMR technique.
Method: Longitudinal prospective study including all treatment naive patients with DAA therapy for HCV eradication during 2018 in the Gastroenterology Department at the Hospital Miguel Servet (Zaragoza. Spain). Lipid and lipoprotein profiles were characterized before and after DAA treatment, as well as at the SVR48 using the routine method and by 2D-DOSY NMR (Liposcale test, Biosfer Teslab). This technique determines the size and number of particles for all subclasses of VDLD, LDL and HDL allowing better characterization of their atherogenic risk.
Results: By November/2019 we have completed the follow-up of 77 DAA-treated patients: 39 (51%) F1, 13 (17%) F2, 14 (18%) F3, 9 (12%) F4. 54.5% women. The median age was 55 years (range 33–83). The eradication of HCV increased the concentration of total and LDL-cholesterol (p = 0.021 and p = 0.003 respectively), as well as the LDL/HDL ratio (p = 0.022) after treatment and then until the SVR48. Total triglycerides and HDL-cholesterol levels did not changed. The number of VLDL and LDL particles also increased significantly at the end of the treatment and at the SVR48, especially the small LDL, the ones with the highest atherogenic risk (p < 0.0001; table 1).
Conclusion: Eradication of HCV with DAA causes lipid changes at the end of the treatment that persists after one year. The characterization of lipoproteins by NMR detects an increase in small LDL particles that might increase the atherogenic risk of DAA-treated patients.

FRI458
Development or worsening of esophageal varices in patients with cirrhosis after DAA-induced HCV clearance

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Background and Aims: Use of direct acting antivirals (DAAs) has allowed to clear HCV in almost all patients even in the presence of advanced cirrhosis. Although it has been suggested that cirrhotic portal hypertension may regress after SVR, the ultimate effect of HCV clearance on the development and progression of esophageal varices (EV) is still unexplored. We assessed in a prospective cohort of patients with cirrhosis the evolution of endoscopic features of portal hypertension after SVR obtained by DAA.
Method: We analysed 207 consecutive patients (mean age 67.8 ± 9.5, males 53%) with HCV Child-Pugh A5-A6 cirrhosis treated with DAAs between January 2015 and May 2016. All patients underwent esophagogastroscopy (EGS), liver ultrasound (US), liver stiffness measurement (LSM) by Transient Elastography and laboratory tests before the starting DAAs and after achieving SVR. LS * spleen diameter/platelet ratio (LSPS) and RESIST-HCV criteria (Albumin >3.6 g/dl and PLT > 120000 mmc) were evaluated as previously described (1,2).
Results: Thirty-eight patients were excluded from the analysis, 28 (13.5%) since they had F2/F3 EV at baseline and were treated with beta-blockers (BB), 5 (2.4%) died during follow up and 5 developed HCC (2.4%). Overall, 169 SVR patients were analysed. At baseline, 42 patients (24.9%) did not have EV and 127 (75.1%) had small EV. None received beta-blockers. After a median of 37 months EGS showed *de novo* development of EV (dimension/occupation ≥ 10%) in 4/42 (9.5%) patients and progression from F1 to F2/F3 EV in 14/127 patients (11%), p = 0.69 by Kaplan Meier. By Cox univariate regression analysis, age, PLT count, spleen diameter, LSPS and RESIST-HCV criteria were associated with EV progression (p < 0.05 for all). At multivariate model, RESIST-HCV criteria (HR: 0.21, CI95%:0.05–0.95, p = 0.04) and younger age (HR: 0.95, CI95%: 0.92–0.99, p = 0.035) were associated with a lower risk of EV progression. Gender (p = 0.93), BMI (p = 0.84) and diabetes (p = 0.24) did not correlate with progression of EV.
Conclusion: Progression of clinically significant portal hypertension, as assessed by the evolution of esophageal varices, is not uncommon among patients with HCV cirrhosis after HCV clearance. Non-invasive, simply algorithm including only albumin and PLT count can assist in identifying patients in whom portal hypertension is likely to progress notwithstanding SVR.

Table 1: (abstract: FRI457): Lipid profile characterization

Variable	Basal	Post-tto	SVR	SVR 48	P*
Lipid concentrations (median [interquartilic range])					
Total cholesterol mg/dl)	187 [162;222]	206 [177;242]	216 [170;244]	216 [178;248]	**0.021**
LDL	112 [91.8;136]	130 [106;164]	135 [107;169]	141 [108;156]	**0.003**
HDL (mg/dl)	53.0 [47.0;66.0]	54.0 [45.0;63.0]	52.0 [45.0;62.0]	55.0 [48.0;67.0]	0.498
Non-HDL cholesterol (mg/dl)	129 [108;156]	152 [125;183]	156 [125;190]	160 [119;178]	**0.003**
LDL/HDL Ratio	3.20 [2.70;4.30]	3.70 [3.20;4.40]	3.80 [3.10;4.80]	3.70 [3.20;4.60]	**0.022**
Number of particles (media [confidence interval 95%])					
LDL (nmol/l)	1238 [1179;1297]	1379 [1310;1448]		1396 [1323;1469]	**<0.0001**
VLDL (nmol/l)	39.6 [33.9;45.3]	41.4 [35.9;46.9]		48.5 [39.5;57.5]	**0.007**
Small LDL (nmol/l)	680 [652;708]	748 [711;784]		777 [733;822]	**<0.0001**
HDL (μmol/l)	27.9 [26.4;29.5]	27.2 [25.8;28.6]		28.2 [26.8;29.6]	0.2776

*P value for the longitudinal variation with a mixed lineal model.

References

1. Berzigotti A et al. Elastography, Spleen Size, and Platelet Count Identify Portal Hypertension in Patients With Compensated Cirrhosis. Gastroenterology 2013;144:102–111.
2. Calvaruso V et al. Is Transient Elastography Needed for Noninvasive Assessment of High-Risk Varices? The REAL Experience. Am J Gastroenterol 2019;114:1275–1282.

FRI459

Partial restoration of brain structural and connectivity changes after HCV cure with direct acting antivirals (DAA)

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Background and Aims: HCV infection is associated with neuropsychiatric manifestations. Previous neuroimaging studies showed brain connectivity dysfunction among HCV patients. The aim of this study was to assess, by magnetic functional resonance in resting state (fMR), the potential structural and connectivity changes before and after HCV eradication with DAA, along with clinical parameters.
Method: Inclusion of HCV-infected patients(≤55 years) with no baseline psychiatric disease, eligible for DAA therapy. Clinical and brain MR evaluation (T1 and fMR) were done at baseline(BL) and after viral cure(FU12). Comparisons were made between HCV patients at BL/FU12 and compared with a non-HCV control group by means of paired/independent T-test analysis. Variables were expressed as n(%); median/$IQR_{(25-75)}$. Brain volume and local gyrification index(LGI) were assessed in T1; functional connectivity was assessed by seed-based analysis (region of interest: left insula). Depression and neurotoxicity were assessed by means of MADRS/PHQ9 and neurotoxicity rating scales, respectively.
Results: Twenty-one HCV patients and 25 controls were included. Among HCV patients: 52% female, age 46 years, RNA-VHC 6.03 $\log_{10}$ (IU/L), elastography 5.2 Kpa (4.3–6), ALT 61UI/L (25–87). DAA were used for 8–12 weeks with 100% cure rate. HCV patients presented significant improvements after HCV cure (FU12) in depression/neurotoxicity parameters compared to BL ($p < 0.01$). HCV (BL and FU12) patients showed a reduced volume in a right lateroccipital area compared to controls (CWP<0.005) (Fig.1A); this volumetric difference was smaller between FU12-HCV and controls. Moreover, LGI was significantly higher in FU12-HCV patients compared to BL-HCV (CWP<0.0005). The connectivity analysis showed a high association of the insula with occipital/parietal territories among HCV patients, compared to controls; this difference in connectivity was higher among BL-HCV and controls, whereas differences were limited to the occipital areas among FU12-HCV and controls (Fig.1B)
Conclusion: Left insula is disturbed among HCV infected patients in structure(gyrification) and connectivity(mainly concerning the occipital area, where a volume reduction was also observed). After HCV cure, differences with controls were reduced, suggesting a partial restoration of brain connectivity. Clinical parameters assessing depression and neurotoxicity improved consistently after HCV cure

Liver tumours: Experimental and pathophysiology

FRI460

Glycogen synthase 2 (GYS2) restricts tumor metastatic ability via attenuating autophagy and breaking glycogenic homeostasis in hepatocelluar carcinoma

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Background and Aims: Aberrant metabolic reprogramming tightly linked to carcinogenesis or tumor progression. However, rare attention has been paid to glycogen metabolism. The regulation of glycogen in liver, as the main organ of glycogen metabolism, might be different to other organs with unknown mechanisms. Here we are willing to demonstrate that Glycogen synthase 2 (GYS2) restrict tumor metastatic ability via attenuating autophagy and breaking glycogenic homeostasis in hepatocellular carcinoma.
Method: GYS2 expression pattern was investigated by both **weighted gene co-expression network analysis** and **Robust Rank Aggregation method** and verified by RT-qPCR, westernblot and immunochemistry in HCC tissue. MTS, metastasis mouse model, transwell assay and tandem mCherry-GFP-LC3 fusion protein assay

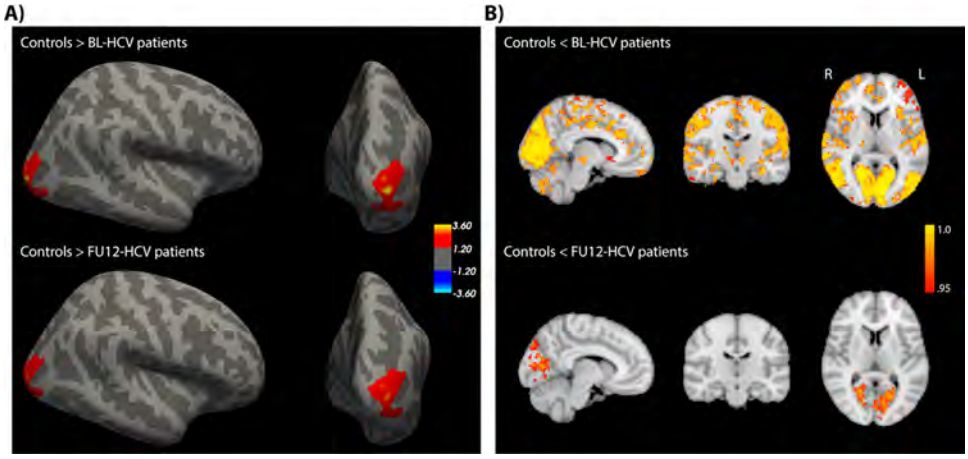

Figure: (abstract: FRI459)

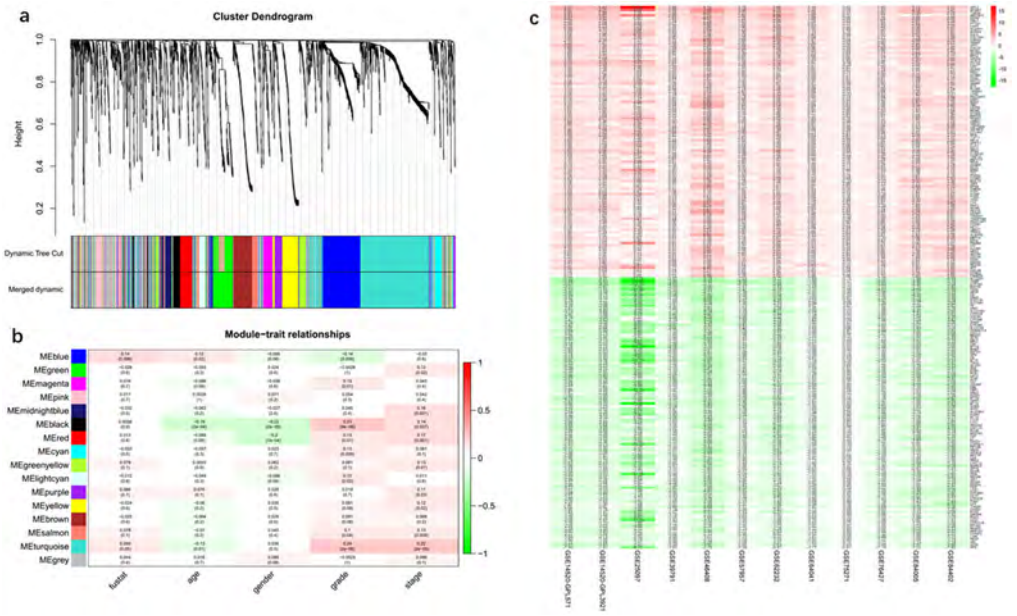

Figure: (abstract: FRI460)

were utilized to assess the function of GYS2 on proliferation, metastasis and autophagy of HCC cells in vitro and in vivo.
Results: GYS2 downregulation was quite prevalent in HCC tissues and closely correlated with worse overall survival. Furthermore, GYS2 overexpression significantly suppressed cell growth, migration and autophagy, the expression of ZEB1, Snail, βcatenin, and increased E-cadherin level. Overexpression of GYS2 induced a decline of PYGL even in starvation condition, consequent glycogen accumulation led to increased reactive oxygen species (ROS) levels and celluar senescence.
Conclusion: In summary, our findings suggested that GYS2 serves as a prognostic factor and functions as a tumor suppressor by inhibiting autophagy and interpreting glycogenic homeostasis in HCC. GYS2 might be a promising target for prevention, treatment and prognostic prediction of HCC.

FRI461

EIF4EBP3, methylated in gastric cancer, acts as a tumor suppressor restraining tumor proliferation and liver metastasis via targeting EIF4E/B-catentin axis

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Background and Aims: Epigenetic aberrations of tumor suppressor genes (TSGs), particularly DNA methylation, are frequently involved in the pathogenesis of gastric cancer (GC). Through a methylome study, we identified eIF4EBP3 as a methylated gene in GC. However, the role of eIF4EBP3 in GC progression has not been explored.
Method: The expression and promoter region methylation of eIF4EBP3 in GC and healthy tissues were analyzed in public datasets. eIF4EBP3 expression in GC was detected by semi-quantitative RT-PCR, western blot and immunohistochemistry. The clinical significance of eIF4EBP3 was analyzed. We also studied epigenetic alterations and functions in GC. The effects of eIF4EBP3 on cell proliferation, migration and invasion were conducted by functional experiments in vitro and in vivo, and epithelial-mesenchymal transition markers were analyzed. Label-free proteomic analysis was applied to identify targets of eIF4EBP3 using Vector/ eIF4EBP3 SGC7901 cells, and functional experiments were performed to confirm a selected target.
Results: The mRNA levels of eIFEBP3 were downregulated in gastric cancer due to promoter region CpG methylation, which was associated with poor survival and tumor progression in GC patients. Ectopic expression of eIFEBP3 significantly inhibited tumor cell growth, migration and invasion both in vitro and in vivo. Label-free proteomic analysis indicated eIFEBP3 downregulated the protein level of β-catenin, which was confirmed by western blot. Overexpression of β-catenin reversed the inhibitory effects of eIFEBP3 on cell growth and migration, indicating that eIFEBP3 acts on GC cells by targeting the eIF4E/β-catenin axis. These observations demonstrate that eIFEBP3 downregulation is a common event in GC specimens and is closely correlated with cancer proliferation and liver metastasis and that EIFEBP3 restrains EMT by a β-catenin-mediated signaling pathway.
Conclusion: These results suggest that eIFEBP3 is a novel TSG methylated in gastric cancer that may play important roles in GC development and liver metastasis and indicate eIFEBP3 as a potential metastasis and survival biomarker for GC.

FRI462

Molecular characterization of hepatocellular carcinoma in Mongolia delineates unique genomic features

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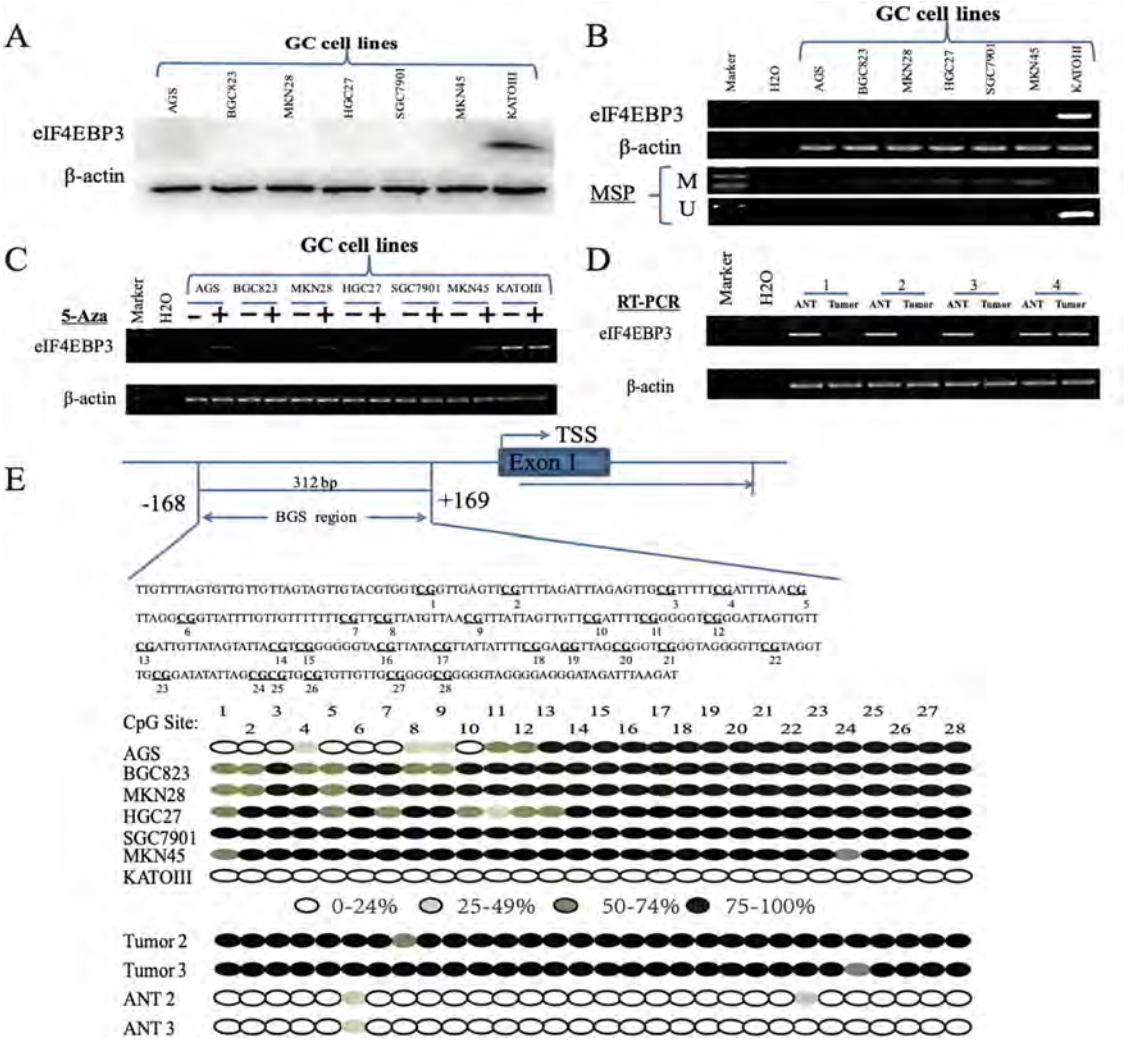

Figure: (abstract: FRI461)

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Background and Aims: Mongolia has the world's highest incidence of hepatocellular carcinoma (HCC), (~100 cases/100,000 inhabitants/year). We aim to perform a molecular characterization of HCC in this country.

Method: 192 paired fresh-frozen HCC/non-tumoral samples from patients undergoing resection in Mongolia were analyzed. Whole exome sequencing (WES) and RNAseq were performed in 151 and 106 samples, respectively. WES was used for mutation calling, mutational signatures (MutSig) analysis, and tumor mutational burden (TMB, mut/Mb) evaluation. The Mongolia cohort was compared to a Western cohort (n = 187) and to an Eastern cohort (n = 231) [*Ahn et al, Hepatology 2014*] to evaluate differences in the genomic profile.

Results: Mongolian patients, compared to Western, were younger (61 vs 66 years old), with lower male predominance (54% vs 80%), and less advanced hepatic fibrosis (F3-4, 38% vs 79% (all $p < 0.001$). Etiologies in Mongolia were: 30% hepatitis C virus (HCV), 9% hepatitis B virus (HBV), 40% HBV coinfection with hepatitis delta virus (HBV/HDV), 6% triple infected (HBV/HCV/HDV), and 15% non-infected. HDV was detected in 84% of HBV-infected samples in Mongolia and 7% in the Western cohort ($p < 0.001$). All HBV+ and HDV+ patients in Mongolia were infected by genotype D and 1, respectively. Unique molecular features were identified in Mongolian HCC: a) Distinct molecular classes: 3 Mongolian classes were identified. MGL1 class (44%) was associated to HCV infection (32% vs. 7%/3%) in older patients (62 vs. 56 years old) ($p < 0.05$), and recapitulate the S3 Western subclass ($p = 0.001$). MGL2 (26%) and MGL3 classes (30%) were enriched with HBV/HDV infection (93%/97% vs. 60%, $p < 0.001$). MGL2 class showed a female/male ratio of 2:1, and clinical (e.g. higher AFP > 400) and molecular features of aggressiveness (i.e. Proliferation classes). MGL3 was enriched with immune features, both from adaptive and innate immune response. b) Mongolian compared to Western and Eastern cohorts showed higher TMB (4 mut/Mb vs. 2.1 vs. 2.3, respectively, $p < 0.001$), without differences among etiologies, and more mutations in *TP53* (46% vs. 32% vs. 27%), *ARID1A* (17% vs. 10% vs. 3%), and *TSC2* (9% vs. 1% vs. 3%), ($p < 0.05$). c) MutSig 3, associated with DNA double-strand break-repair, and MutSig22, associated with aristolochic acid exposure, were detected in 34% and 11% of samples in Mongolia and 5% and 3% in the Western cohort ($p < 0.001$).

Conclusion: HCC in Mongolia shows unique molecular traits, including a) distinct molecular classes, two of which relate to HBV/HDV infection and younger age, b) higher number of mutations per tumor and c) high prevalence of a mutational signature related to DNA repair, suggesting the presence of a distinct genotoxic agent in this country.

FRI463

NK-cell dysfunction in hepatocellular carcinoma: modulatory approches for functional restoration

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Background and Aims: Several immune mechanisms contribute to an immunosuppressive tumour immune milieu: regulatory immune cells, checkpoint receptors, low nutrients and hypoxia that can affect immune cells metabolism and function. Metabolic profiles rather than phenotypic characteristics seem to define the functional role of NK cells and their influence in a correct anti-tumour effect. NK-cell response is functionally impaired in Hepatocellular Carcinoma (HCC), however little is still known about NK-cell metabolism in this tumour.
Method: Liver and tumour infiltrating lymphomononuclear cells from 10 patients were derived from surgical specimens and NK-cells were purified by flow activated cell sorting in order to perform gene expression profiling. NK-cell phenotype, glucose uptake and mitochondrial polarization were defined by multi-parametric flow cytometry. Modulatory compounds were identified on the basis of gene expression profiling and employed to restore tumour infiltrating NK-cells metabolism and cytotoxic functions.
Results: Genome-wide expression profiling showed enrichment of upregulated genes belonging to metabolic pathways in HCC-infiltrating NK cells: glycolysis and oxidative phosphorylation, cell cycle, DNA damage and p38-related pathway. Higher level of phosphorylated-p38 protein was confirmed in tumour infiltrating NK cells while phenotypic characterization showed enrichment of CD49a positive and CD27CD11b double negative NK-cells that has been associated with regulatory and dysfunctional NK-cells. Functional and metabolic assessment showed defective degranulation capacity, reduced autophagy and glucose consumption. Targeting MAPK pathway by two different p38-inhibitors could restore NK-cell functions.
Conclusion: We identified an impairment of energy metabolism of HCC-infiltrating NK-cells associated with functional defects that can be rescued modulating MAPK pathway. These results provide the basis to develop new strategies to potentiate NK-cell response in HCC.

FRI464

Global characterisation of tumour infiltrate of intrahepatic cholangiocarcinoma by single cell sequencing

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Background and Aims: Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary liver cancer, characterized by high resistance to chemotherapy and poor prognosis. We have previously demonstrated that the tumor immune microenvironment (TME) has a prognostic impact on iCCA patients; however, little insight exists on immune subsets involved in iCCA and precise criteria to assess tumor biology are still lacking.
Method: we examined immune infiltrate with single cell-RNA sequencing (scRNAseq) of iCCA tumor and peritumor liver sample. scRNAseq was performed on CD45+ sorted cells isolated from tumoral and peritumoral sample of iCCA patients (n = 6) surgically resected at the Division of Hepatobiliary and General Surgery in Humanitas. Cell suspensions were converted to barcoded scRNAseq libraries with 10× Genomics Chromium Single-cell system and were sequenced on Illumina NextSeq 500. CellRanger (v3.0.1, 10× Genomics) pipeline were applied to obtain gene espression data. For each cluster, gene average expression and marker genes were obtained. A principal component analysis (PCA) was performed both for the whole dataset and for each cluster of cells. Clusters classification by cell types was performed by comparing each single cell gene expression with public transcriptomic datasets of pure cell types by using the SingleR (v0.9) Bioconductor R package.
Results: We obtained an integrated dataset of 12 samples for a total of more than 30,000 good quality single cells with a median of 800 detected genes each. This analysis revealed that tumor samples clearly separate from peritumoral ones according to the main principal immune cells population for each patient. Key actor of these differences, identified by clustering and classification analysis, were T cells, NK cells and myeloid cells. Moreover, each of them is characterized by cell subpopulations with transcriptional differences between tumoral and peritumoral samples.
Conclusion: These results highlighted that TME strongly differs from the immune system infiltrating the peritumoral area. Further, our study provides a new approach for patient stratification and will help further understand the functional states and dynamics of TME in iCCA.

FRI465

New prognostic score utilizing glypican-3 serum levels for the prediction of 6-month outcome after transarterial therapies for patients with intermediate stage hepatocellular carcinoma

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Background and Aims: The selection of patients with intermediate stage hepatocellular carcinoma (HCC) for transarterial therapies currently relies on liver function and tumor properties. Outcome prediction by circulating biomarker is desirable, but not established. The aim of this study was to assess experimental HCC biomarkers for their association with survival after transarterial therapies.
Method: Data were retrospectively collected from 125 consecutive HCC patients with intermediate stage HCC (BCLC-B) undergoing either transarterial chemoembolization (TACE, n = 98) and/ or selective internal radiation therapy (SIRT, n = 28) at one German University Hospital between 2010 and 2017. Patients and tumor

characteristics including total diameter and number of tumor lesions, C-reactive protein (CRP), platelets, leucocyte counts, albumin, bilirubin and alanine transaminase (ALT) levels as well as circulating HCC biomarkers including AFP, AFP-L3, des-gamma-carboxy prothrombin (DCP), alone and summarized in the GALAD score, glypican-3 (GPC-3), and Dickkopf-related protein 1 (Dkk-1) were quantified on cryopreserved serum samples taken prior to therapy. Univariate and multivariate analyses were performed to identify the predictive value of the different biomarkers for 6-month survival. The parameters with the strongest independent association with survival were included into a new scoring system.

Results: Univariate analyses showed that lower GPC-3 as well as DCP serum levels were significantly associated with 6-month survival (median GPC-3: 8 pg/ml vs. 32 pg/ml, p = 0.002; DCP: 4 ng/ml vs. 16 ng/ml, p = 0.004). Moreover, higher GALAD-scores were associated with a poorer prognosis (4.85 vs. 1.32, p = 0.008). In contrast, all other patient and tumor related parameters showed no significant difference regarding 6-month survival.

By multivariate analysis, the biomarkers with the highest association with treatment response were GPC-3, the number of lesions and CRP. A combination of the three markers in a new prognostic score GLC (GLC = 2.873–2.161/100 * **G**PC-3 (pg/ml) - 0.185 * number of **l**esions - 0.052 * **C**RP (mg/l))was developed resulting in a specificity of 72.7% and sensitivity of 77.9% for prediction of 6 months survival (Fig. 1).

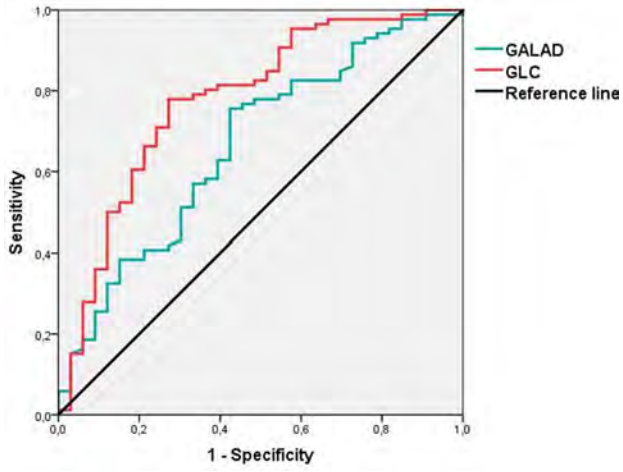

Fig 1 Receiver operating characteristic (ROC) analysis of sensitivity and specificity by the GALAD and the GLC score in predicting 6-month-survival.

Conclusion: The combination of novel HCC biomarkers might be a potent tool for tailoring individualized treatment strategies for patients with intermediate stage HCC. The GLC-Score can help to estimate the 6-month-survival rate of these patients with high sensitivity and specificity. A GLC-Score above 1.4 is associated with a 6-month survival rate of 80%.

FRI466

Ganglioside patterns in the human cholangiocarcinoma stem cell subset

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Background and Aims: Cancer stem cell (CSC) represents a critical therapeutic target in neoplastic diseases. Gangliosides (GS) are a family of sialic acid–containing glycosphingolipids, which have been associated with the malignant phenotype of several cancers (i.e. breast, melanoma, glioblastoma, ovary). Recent evidence indicates the possible involvement GS in tumor stem cell biology, but no data regarding GS composition in human cholangiocarcinoma (CCA) are available. The aim of this study was to provide a GS profiling of the stem-like subset and of their parental cells in human CCA.

Method: Stem-like subset was enriched by sphere culture (SPH) using well-established human intrahepatic CCA cells (HUCCT1, CCLP1). CCA GS patterns were analyzed by chromatographic procedures. Assessment of GS turnover and identification of GS molecular species were evaluated using 3Hsphingosine. The role of GS in the modulation of stem features was investigated using D-threo-1phenyl-2-palmitoylamino-3-N-morpholine-1-propanol (PPMP), a GM3 synthase inhibitor. FACS-sorted GD2+ SPH cells were examined for stem-like gene expression compared to GD2- SPH.

Results: In both CCA lines, the amount of total GS was markedly different comparing parental cells grown in monolayer conditions (MON) and their stem-like subsets (SPH). CCA-SPH showed enrichment in the major GS class (GM3), reduction of GM2 and the presence of GD2. This was corroborated by high expression levels of GM3 synthase as well as of GD3 and GM2/GD2 synthases in CCA-SPH. Enzymes involved in GS biosynthesis were strongly expressed in CCA-SPH compared to MON. Notably, sphere-forming ability and expression of CSC-related genes were reduced in cells treated with by PPMP. Likewise, GD2+ SPH cells were enriched with CSC-markers (CD133, EpCAM, CD44) and expressed at higher levels several genes involved in pluripotency, self-renewal and epithelial mesenchymal transition compare to GD2- SPH. Notably, expression of GM2/GD2 synthases was significantly increased in tumor samples compared to paired non-tumoral tissue of CCA patients (n = 104) and significantly correlated with the presence of satellite nodules, lymph node invasion and recurrence.

Conclusion: We show for the first time that the CCA stem-like properties may be associated with modification in the GS synthetic pathway.

FRI467

T cell exhaustion dynamics are linked to clinical outcomes in hepatocellular carcinoma

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Background and Aims: Hepatocellular Carcinoma (HCC) is the major cause of liver cancer, a major global health problem with limited treatment options and poor prognosis. The immunobiology of hepatocellular carcinoma is poorly understood. Exhausted and liver-resident T cells have been identified in HCC patients but their role and clinical relevance remained unclear. We therefore aimed to assess the clinical impact of exhausted T cells in HCC patients by using a system immune profiling approach based on newly developed transcriptomic and cytometric signatures.

Method: Comprehensive phenotypic and functional exhaustion profiling of the peripheral and intrahepatic immune compartment (tumor-surrounding and tumor microenvironment) was performed ex vivo on samples from 20 HCC patients using flow and mass cytometry. Single-cell- and population based transcriptome profiles from published datasets of HCC resections were *in silico* assessed for signatures of T cell exhaustion and residency and their link to patient survival. Exhaustion and residency of exhausted T cells were further analyzed by immunohistochemistry.

Results: We found that exhausted T cells can be identified in the peripheral blood and enriched in the liver of HCC patients. High-parametric phenotypic and functional analysis identified significantly exhausted CD8+ T cells in the tumor microenvironment. Importantly, a strong enrichment of more exhausted subtypes of CD8+ T cells with differential expression of multiple immune checkpoint targets in the tumor microenvironment at the expense of liver resident memory T cells and cytotoxic T cell signatures was negatively linked to patient survival. These findings were confirmed by *in silico* analysis of exhaustion and residency signatures in TCGA HCC samples.
Conclusion: These data underline the clinical relevance of the exhausted T cell response in HCC patients. The dynamics between exhausted and resident liver T cells have implications for immune-based diagnostics, rational patient selection and monitoring during HCC immunotherapies.

FRI468
Lactate promotes invasion and metastasis of hepatocellular carcinoma via changes in mitochondrial and histone acetylation
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Background and Aims: Acidosis is nowadays considered as a hallmark of human cancers. We previously found that lactate secreted by cancer associated hepatic stellate cells (HSCs) was a major source to form acidosis microenvironment in hepatocellular carcinoma (HCC). However, the mechanism underlying lactate promotes HCC malignant progression was not fully demonstrated.
Method: Glucose metabolism reprogramming (glucose uptake ability, oxygen consumption rate, lactate accumulation) of HSCs, invasive ability and acetyl-CoA content of HCC cells were detected in the HCC-HSCs co-culture model. ^{14}C labeled lactate was introduced to trace the contribution to downstream carbon metabolic intermediates. The expression and acetylation levels of mitochondrial pyruvate carrier 1 (MPC1) were measured to determine the degradation of MPC1 in HCC cells. In addition, the acetylation levels of H3K27 and key transcription factor TWIST2 of HCC cells were detected. The therapeutic effect of combination of acetyltransferase p300 inhibitor C646 and monocarboxylate transporter 1 (MCT1) inhibitor CHC were determined by invasive ability *in vitro* and lung metastasis *in vivo*.
Results: Glucose metabolism reprogramming of HSCs was occurred from oxidative phosphorylation to glycolysis, especially characterized by large amount of lactate secretion, after co-cultured with HCC. Furthermore, ^{14}C labeled lactate tracer was used and found that mitochondrial proteins and histone were hyperacetylated. In detail, MPC1 was acetylation modified and subsequently degraded, leading to decreased mitochondrial pyruvate uptake and increased glycolysis in HCCs. Meanwhile, lactate activated *TWIST2* expression indirectly by promoting H3K27 acetylation on the *TWIST2* promoter, mediated by histone acetyltransferase p300. Moreover, combination of acetyltransferase p300 inhibitor C646 and MCT1 inhibitor CHC could remarkably inhibit invasion and metastasis of HCC.
Conclusion: In this study, our work revealed that acidosis microenvironment shaped by lactate promoted invasion and metastasis of HCC by regulating acetylation of MPC1 and H3K27. Thus, lactate blockade might be a potential metabolism-based target to enhance the therapeutic efficacy.

FRI469
Dysregulation of aquaporin-1 in human CCA cells triggers epithelial-mesenchymal transition
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Background and Aims: Cholangiocarcinoma (CCA) is a tumor arising from biliary epithelial cells. The overall prognosis is very poor due to the ability of the tumor to develop chemoresistance and metastasis. Epithelial-mesenchymal transition (EMT) is a multistep process during which epithelial cells gradually adopt structural and functional characteristics of mesenchymal cells. EMT is required for tumor cell migration, invasion and has been considered an early event of metastasis. EMT occurs in CCA where is associated with progression and chemoresistance. The function of aquaporin (AQP) water channels in tumors has been the focus of substantial research efforts. However, the role of AQPs in liver cancers and specifically in CCA remains unknown. Our aim was to study the role of aquaporin-1 (AQP1) in the regulation of EMT in CCA.
Method: Two established human CCA cell lines, HuCCT1 and KMCH, were used as experimental models. We generated KMCH AQP1 shRNA knock-down and HuCCT1 AQP1 KO by CRISPR/Cas9 system. Cell proliferation and migration were assessed by the Incucyte live-cell imaging system. We performed an unbiased discovering experiment using RNAseq comparing wild-type and AQP1 KO CCA cells. EMT and stemness markers expression were evaluated by RT-qPCR, western-blot and confocal microscopy.
Results: Both CCA cell lines express AQP1 largely located in intracellular compartments. Dysregulation of AQP1 in tumor cells significantly induces proliferation and migration, suggesting a tumor suppressor role of AQP1 in CCA. RNAseq of AQP1 KO cells showed a total of 2702 differentially expressed genes. The Ingenuity Pathway Analysis showed Cancer (p-value range 3.36E-04-9.16E-34), Cellular movement (p-value range 2.54E-04-1.71E-20), and Cellular Growth and Proliferation (p-value range 2.23E-04-3.34E-11) as the top affected Diseases and Biological functions. In addition, the epithelial markers genes were significantly downregulated upon AQP1 silencing (E-cadherin gene *CDH1* by −133 fold change; $p < 0.001$, cytokeratin19 gene *KRT19* by -8 fold change; $p < 0.001$), while mesenchymal markers genes were significantly upregulated (vimentin gene *VIM* by 4 fold change; $p < 0.001$, fibronectin gene *FN1* by 3.51 fold change; $p < 0.001$), suggesting that the loss of AQP1 induced EMT. Furthermore, these changes were corroborated at mRNA and protein levels, with a major E-cadherin downregulation along with an upregulation of mesenchymal markers vimentin, fibronectin and EMT-inducing transcription factors ZEB1 and ZEB2.
Conclusion: Our data suggest that AQP1 acts as a tumour suppressor in CCA cells by acting both on proliferation and migration through an EMT process. Therefore, AQP1 might have an important role by restraining CCA progression.

FRI470
Diagnostic performance of PIVKA-II in patients with hepatocellular carcinoma
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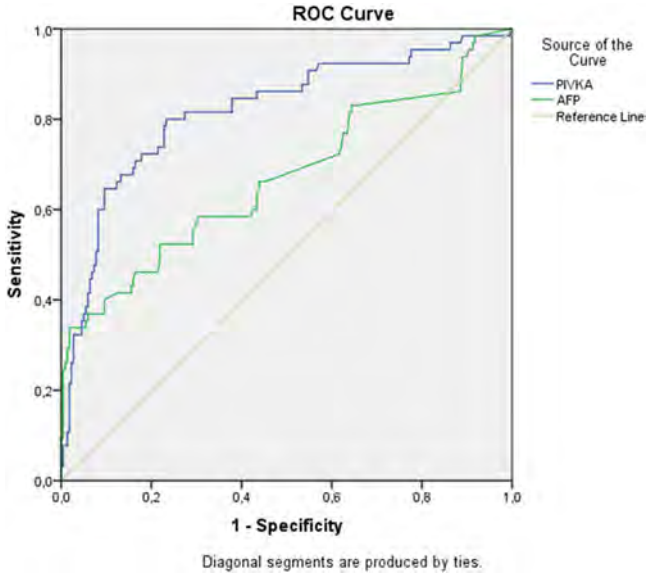
Background and Aims: Hepatocellular carcinoma (HCC) represents the second leading cause of cancer deaths worldwide. HCC has a silent course making clinical diagnosis often delayed, with a significant impact on prognosis. Protein induced by vitamin K absence (PIVKA-II) has been proposed as a potential biomarker for HCC. This study has been designed to evaluate the role of PIVKA-II in the diagnosis of HCC through the comparison between PIVKA-II and alpha-fetoprotein (AFP) serum levels on HCC patients and the two control groups of patients with liver disease and without HCC.
Method: In an Italian prospective cohort, PIVKA-II levels were assessed on serum samples by an automated chemiluminescent immunoassay (Abbott ARCHITECT). The study population included 65 patients with HCC (both "de novo" and recurrent), 111 with liver cirrhosis (LC) and 111 with chronic hepatitis C (CHC). The diagnostic accuracy of PIVKA-II for HCC diagnosis was assessed by the receiver-operating characteristic (ROC) analysis.
Results: PIVKA-II levels were increased in patients with HCC (median 63.75, range: 12–2675 mAU/mL) compared to LC (median value: 30.95, range: 11.70–1251 mAU/mL, Mann Whitney test $p < 0.0001$) and CHC (median value: 24.89, range: 12.98–67.68 mAU/mL, $p < 0.0001$). The area under curve (AUC) for PIVKA-II was 0.817 (95% Confidence Interval (CI), 0.752–0.881). At the optimal threshold of 37 mAU/mL, identified by the Youden Index, the sensitivity and specificity were 79% and 76%, respectively. PIVKA-II was a better biomarker than AFP for the diagnosis of HCC, since the AUC for AFP was 0.670 (95% CI 0.585–0.754, $p < 0.0001$) and at the best cutoff of 16.4 ng/mL AFP yielded 98% specificity but only 34% sensitivity. PIVKA-II and AFP presented a low degree of correlation (Spearman $r = 0.15$, $p = 0.013$) and no correlation at all in the HCC group ($r = 0.016$). The combination of PIVKA-II and AFP reached positive and negative predictive values of 100% and 85%, respectively. The sub-analysis of HCC population showed that PIVKA-II values were significantly higher in Barcelona Clinic Liver Cancer (BCLC) stage B than in BCLC A (median 211.48 vs. 59.28, $p = 0.0013$) and in BCLC 0 (median 55.13, $p = 0.02$)



Conclusion: These initial data suggest the potential utility of this tool in the diagnosis of HCC. PIVKA-II alone or in combination may help to an early diagnosis of HCC and a significant optimization of patient management.

FRI471
TGF-beta-associated circular RNAs in cholangiocarcinoma: mechanisms and biomarkers

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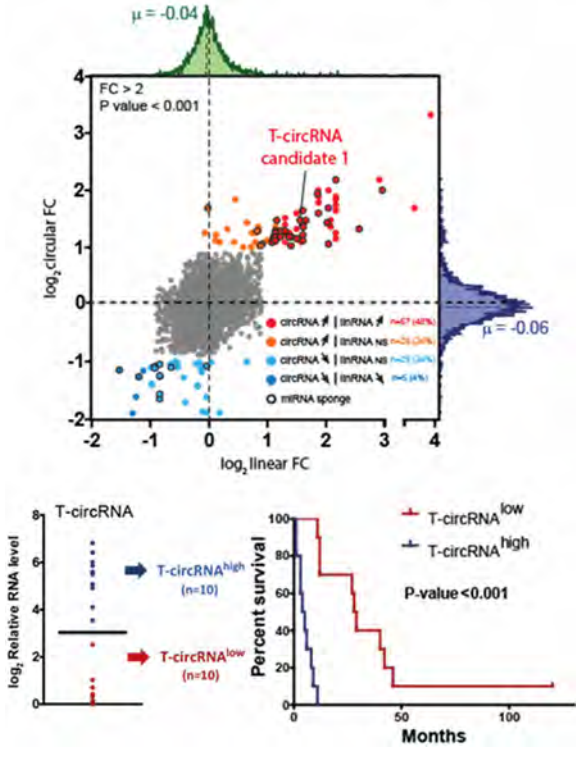
Background and Aims: Cholangiocarcinoma (CCA) is a deadly cancer worldwide, as a result of increased incidence and limited therapeutic options. Transforming growth factor beta (TGFb) plays a key role in hepatobiliary cancer and interfering with this pathway represents a clinically relevant therapeutic strategy. However, targeting TGFb is complex due to its functional duality (pro-cytostatic at an early stage vs. pro-metastatic at an advanced stage). So far, the molecular mechanisms involved in this functional duality are not fully understood. We hypothesize that non-coding RNA (ncRNAs), including circular RNA (circRNA) and microRNA (miRNA), take part of the TGFb network to switch the actions of TGFb toward metastasis in CCA progression. Thus, we aim at characterizing pro-metastatic TGFb-regulated circRNA acting as miRNA sponges and serving as relevant biomarkers in human CCA.
Method: Unsupervised gene expression profiling (RNA sequencing) was used to identify known and novel TGFb-regulated coding and ncRNA (mRNA, lncRNA, miRNA and circRNA) in human CCA cell lines. A bioinformatics pipeline was developed to identify a TGFb-associated gene regulatory network of coding and ncRNA and to identify circRNA acting as miRNA sponges. Candidates were validated in several CCA cell lines, and their clinical relevance (e.g. survival analyses) was evaluated in a collection of 50 clinically well annotated intrahepatic CCA from the French Liver Network. Exosomes were isolated by ultracentrifugation and validated by electron microscopy and q-Nano.



Results: Genome-scale profiling identified 119 TGFb-regulated circRNA, including T-circRNA1, a novel TGFb-induced circRNA, which displayed 5 binding sites for miR-338, a well-known tumor suppressor miRNA. Hence, T-circRNA1 acts as a competitive RNA keeping away miR-338 from its natural linear targets, including CXCR4, SKIL and SOX4, which results in the overexpression of these pro-metastatic effectors. Analysis of T-circRNA1 expression in resected iCCA tumors demonstrated its prognostic value. Patients with a low T-circRNA1 expression showed a better survival than patients with high T-circRNA1 expression. T-circRNA1 expression was also identified in exosomes upon TGFb stimulation and in the serum of patients.
Conclusion: Our data highlight circRNA as novel regulators of the TGFβ network in CCA. T-circRNA1 induction results in switching the action of TGFβ toward tumor progression. T-circRNA1 constitutes a relevant biomarker in human CCA.

FRI472

Tracking neutrophils within the hepatocellular carcinoma microenvironment - development of relevant orthotopic and ex-vivo 3D liver-HCC culture models

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Background and Aims: Immunotherapies have exciting potential in hepatocellular carcinoma (HCC), given that up to 50% of tumours have an immune component. Despite this, clinical studies indicate that only 15% of HCC patients respond to T cell immune checkpoint inhibitors. Targeting more than one component of the immune microenvironment may improve response rates and our previous work supports neutrophils as drivers of HCC and candidate immunotherapy targets. To better understand the complex role of neutrophils in HCC our aims were to develop models with an immune-rich tumour microenvironment, in which to explore the importance of neutrophils for tumour growth.
Method: Murine liver hepatoma Hep 53.4 cells were implanted via surgical intrahepatic injection into the left lateral lobe of wild type mice. A group of mice also underwent Ly6G antibody mediated neutrophil depletion prior to tumour implantation. Mice were harvested at 10 and 25 days and precision cut liver slice (PCLS) from cores of tumour, peri-tumour and non-tumour tissues created. Slices were kept in a bespoke PCLS bioreactor and rocked under incubation to ensure viability and retention of functionality. Isolated neutrophils were labelled for imaging and added to PCLS prior to multiphoton microscopy to visualise neutrophil uptake within the slices.
Results: Tumours were engrafted in all mice injected with Hep 53.4 cells and progressed up to 2 cm in size at 4 weeks (Figure A). On microscopic examination we noted substantive collagen deposition and stromal formation (Figure B, white lines). FACS sorting of dissociated ex-vivo tumours revealed infiltration by multiple immune cell types including neutrophils. Neutrophil depletion significantly reduced tumour growth. PCLS from diseased livers survived for at least 5 days and added neutrophils migrated through the full thickness of the liver tissue, but preferentially accumulated in peri-tumour regions (Figure B, neutrophils in red).

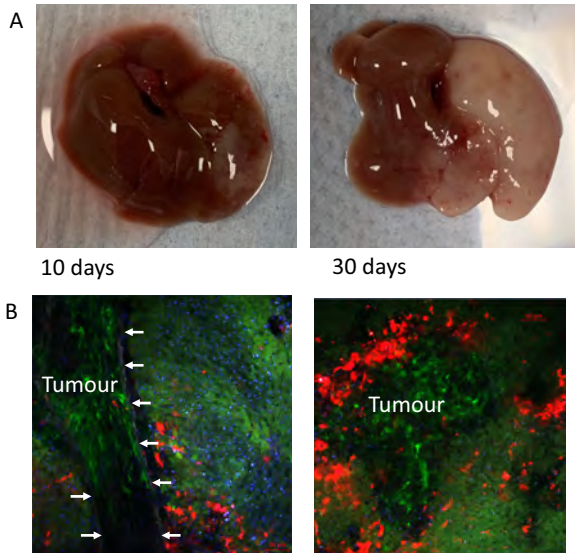

Figure: (abstract: FRI472)

Conclusion: We have developed a new orthotopic model of HCC in mice that becomes populated by a variety of host immune cells. Tumours can also be incorporated ex-vivo in a PCLS-HCC model, designed for drug discovery and mechanistic investigations. The Hep 53.4 model has the advantage of its speed of set up and the opportunity to interrogate effects of manipulation of specific immune cell types including neutrophils, which were confirmed as important drivers of HCC.

FRI473

Identification of PD-L1- expressing exosome-derived microRNAs in human hepatocellular carcinoma

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Background and Aims: Hepatocellular carcinoma (HCC) is one of the most aggressive cancer and the third leading cause of cancer-related death worldwide. Recently, PD-1 and PD-L1 inhibitors, monoclonal antibodies that target either PD-1 or PD-L1, have been widely used in patients with advanced stage HCC. However, response rate of the PD-1/PD-L1 inhibitors is not certain in overall patients, which limits the application in clinical practice. Cancer cell derived exosomes have been evaluated as biomarkers for diagnosis and prognosis in cancers. The aim of this study was to investigate exosomes from high PD-L1-expressing cancer cells and their containing microRNAs (miRNAs) in HCC.
Method: Five HCC cell lines (HepG2, Hep3B, Huh7, SK-Hep-1, and SNU-398) and serum samples from HCC patients were analyzed. Exosomes were isolated from cell culture medium and serum samples using ExoQuick, and it was confirmed by expression of exosome markers (CD9, CD63, and ALIX) based on immunoblotting. PD-L1 protein expression was determined by western blot analysis using anti-PD-L1 antibody. Expression of PD-L1 mRNA and miRNAs were determined by quantitative real-time PCR (qRT-PCR).
Results: We found strong PD-L1 expressing cell lines group (Hep3B, SK-Hep-1, and SNU-398) and weak PD-L1 expressing cell lines group (HepG2 and Huh7). The two cell lines (SK-Hep-1 and HepG2)

displayed consistent PD-L1 expression status in mRNA as well as protein. In further analysis of PD-L1 related miRNAs, 3 exosomal-miRNAs (miR-15a, -16, and -203) were positively correlated and 2 exosomal-miRNAs (miR-21 and -34a) were negatively correlated with PD-L1 expression. We also found significant correlations between PD-L1 expressing exosome numbers and clinicopathological features in serum samples of HCC patients.
Conclusion: We provided the evidence for the potential of exosomal-miRNAs as novel non-invasive circulating markers for prediction of treatment efficacy of anti-PD-1/anti-PD-L1 therapy in HCC patients.

FRI474
Long interspersed nuclear element-1 (line-1) hypomethylation is associated with poor outcomes via the activation of ST18 in human hepatocellular carcinoma
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Background and Aims: The level of long interspersed nuclear element-1 (LINE-1) methylation, representing the global DNA methylation level, could contribute to the prognosis of cancer via the activation of oncogenes. This study was performed to evaluate the prognostic implications of LINE-1 hypomethylation in patients with hepatocellular carcinoma (HCC) and the possible mechanisms related to oncogene activation.
Method: Seventy-seven HCC patients between October 2014 and September 2015 were enrolled in this prospective study. Quantitative pyrosequencing was performed to assess the LINE-1 methylation level of HCC and matched non-HCC tissue samples. The expression of suppression of tumorigenicity 18 (ST18) was measured by immunohistochemistry and its correlation with LINE-1 methylation levels was examined.
Results: LINE-1 was significantly hypomethylated in the HCC tissue compared with the matched non-tumor tissue (64.0 ± 11.6% vs. 75.6 ± 4.0%, $P < 0.001$). LINE-1 hypomethylation was an independent risk factor for overall survival (HR = 27.291, $P = 0.032$) and disease progression (HR = 5.298, $P = 0.005$). The expression of ST18 was higher in the hypomethylated LINE-1 HCC tissue than the hypermethylated LINE-1 tumor tissue ($P = 0.030$).
Conclusion: LINE-1 hypomethylation is associated with poor prognosis in HCC patients, possibly due to the activation of ST18. LINE-1 hypomethylation may serve as a potential prognostic marker for patients with HCC.

FRI475
Tristetraprolin is a key driver of hepatic inflammation, fibrosis and cancer development in vivo
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Background and Aims: Tristetraprolin (TTP) is a key post-transcriptional regulator of inflammatory and oncogenic transcripts. Accordingly, TTP was reported to act as a tumor suppressor in specific cancers. Herein, we investigated how TTP contributes to the development of liver inflammation and fibrosis, which are key drivers of hepatocarcinogenesis, as well as to the onset of hepatocellular carcinoma (HCC).
Method: TTP expression was investigated in mouse/human models of hepatic metabolic diseases and cancer. The role of TTP in non-alcoholic steatohepatitis (NASH) and HCC development was further examined through *in vivo* approaches using liver-specific TTP knock-out mice (LTTPKO mice) and *in vitro* using a panel of HCC hepatic cancer cells.
Results: TTP is downregulated in high-grade human HCC and its loss correlates with poor prognosis. Consistently, we uncover HNF4α as a key regulator of TTP expression and that TTP downregulation is associated with an induction of key oncogenes driving hepatocarcinogenesis. Finally, although TTP overexpression in cultured HCC cancer cells triggers apoptosis and decreases cell migration, TTP loss *in vivo* strongly restrains development of hepatic steatosis and inflammation/fibrosis in mice fed a methionine/choline-deficient diet, as well as HCC development induced by diethylnitrosamine (DEN).
Conclusion: Loss of TTP is a biomarker of high-grade HCC associated with poor prognosis. While TTP displays tumor-suppressive activity *in vitro*, it promotes NASH and hepatic carcinogenesis in mouse *in vivo* models.

FRI476
Identification of neoantigens as potential vaccines in hepatocellular carcinoma
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Background and Aims: Neoantigens, new immunogenic sequences arising because of tumor mutations, have been associated with response to immunotherapy and are considered potential targets for vaccination. Hepatocellular carcinoma (HCC) is a moderately mutated tumor, where the neoantigen repertoire has not been characterized. Our aim was to identify neoantigens in HCC patients, testing their immunogenicity for future use in therapeutic vaccination.
Method: Whole exome sequencing and RNAseq were performed in a cohort of twelve HCC patients submitted to surgery or liver transplant. To identify mutations, single nucleotide variants (SNV) originating non-synonymous changes that were confirmed at the RNA level were analyzed. In silico HLA binding algorithms, in vitro biochemical HLA binding assays and in vivo immunization procedures in HLA class I and class II transgenic mice were used to confirm the generation of neoAgs from mutated sequences.
Results: In an initial group of nine patients, a median per patient of 312 SNV originating missense changes were found, which were narrowed to 21 when considering only those non-annotated in databases and expressed at the mRNA level. HLA binding algorithms predicted a median of 10 and 4 peptides per patient as potential binders to class I and class II molecules, respectively. For HLA-A2.01-predicted binders, binding was experimentally confirmed in 72% of them. While none of the non-confirmed binders resulted immunogenic, immunogenicity was demonstrated in 70% of confirmed binders, generating polyfuctional T cell responses that specifically

recognized the mutated but not the wild-type sequence. Vaccination with longer peptides encompassing these sequences confirmed their immunogenicity and demonstrated their processing in vivo and in vitro. Equivalent results were obtained when analyzing a second group of three patients. In the case of class II HLA-DRB1*01-predicted peptides, 66% of them were confirmed as binders and 45% were immunogenic. Finally, co-immunization experiments combining CD8 and CD4 neoantigen epitopes resulted in stronger CD8 T cell responses.

Conclusion: These results show that mutations arising in HCC tumors may generate neoantigens recognized by CD8 and CD4 T cells, with potential applicability for therapeutic vaccination.

FRI477

SIMBA: a user-friendly high-throughput tool for spheroid invasion analysis of hepatocellular carcinoma cell lines

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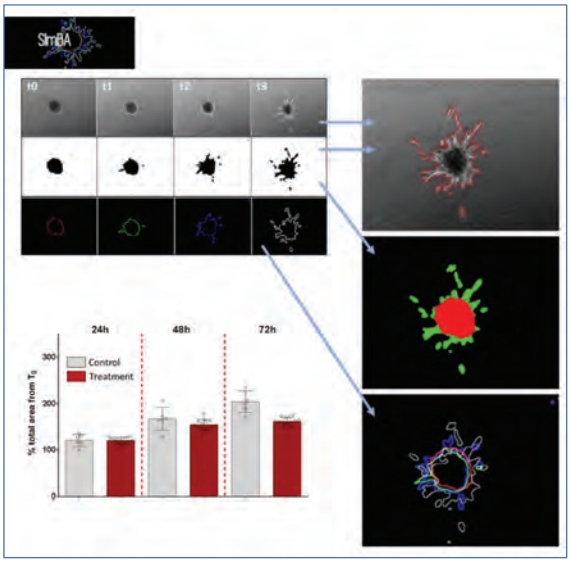
Background and Aims: Due to the complex pathology of hepatocellular carcinoma (HCC) and its asymptomatic early stages, intrahepatic invasion and extrahepatic metastasis to a.o. the lung and abdominal lymph nodes are often already present at diagnosis. The evaluation of treatment effects on HCC invasion in *in vivo* models is currently far from evident[A] and not feasible for high-throughput drug screening. 3D *in vitro* assays such as the spheroid invasion assay (SIA) have already proven their physiological relevance in different cancer types[B] and have been applied in experimental HCC[C]. In order to use SIA in high-throughput screening of HCC drugs, methods for fast and in depth data analysis are required. Accordingly, we developed SImBA (Spheroid Image Batch Analysis), a FIJI-based software tool which allows to perform high-throughput image segmentation, visualization and quantification of invasive spheroids.



Method: Spheroids of two HCC cell lines (HEP3B and SNU423) were embedded in a 3D collagen Type I matrix. Phase contrast microscopy images were recorded at different time points to evaluate the invasive process of control and treated spheroids. Since FIJI is commonly used free software[D], SImBA has been written as an open-source FIJI macro which ensures high user-friendliness and easy customization by the user. SImBA allows batch image processing independent of data set size and is applicable on images of variable and low contrast.

Results: Since SImBA is able to visualize and quantify the invasion data in multiple ways (using total spheroid area, spheroid outlines, area overlaps, montages and a derived invasion index), it allows to robustly demonstrate the effects of various drugs compared to control treatment. Importantly, effects on invasion and cytotoxicity can be linked using SImBA when fluorescent images of cytotoxicity from e.g. Sytox green staining are recorded.

Conclusion: We created a highly functional, easy to use free software tool for the quantitative analysis of high-throughput spheroid invasion and visualization of the invasive capacity of hepatic cancer cell lines. This will contribute to future drug screening in HCC using either 3D SIA or related assays using organoids.

References

1. N P Santos, et al, Tumor Biology, 2017 Mar.
2. Nath S, et al, Pharmacol Ther. 2016 Jul.
3. Khawar IA, et al, Neoplasia, 2018 Aug.
4. https://fiji.sc/.

FRI478

Development of personalised human immunocompetent ex vivo models of primary and secondary liver cancers using precision cut tissue slice technology

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Background and Aims: Experimental models of liver cancers lack the complex interactions between the immune system and tumour, they also fail to capture inter-individual variability, 3D tissue architecture, cellular heterogeneity and tumour specific immune landscape. This has hindered the understanding of the pathogenesis of disease and development of personalised treatment approaches. We aimed to develop ex-vivo human immunocompetent models of primary (hepatocellular carcinoma; HCC) and secondary (neuroendocrine liver metastasis; LM-NEN) liver cancers using precision cut tissue slice (PCTS) technology from surgical waste for discard or explanted tissue.

Method: To date, 6 HCC and 5 LM-NEN tissue samples have successfully been collected and sliced using previously established protocols. PCTS were cultured ex-vivo for 8–15 days in i) 95% O2, ii) atmospheric O2, iii) atmospheric O2 + microfluidic organ-on-a-chip system (CNBio). Each day the viability of slices was assessed by measuring apoptotic vs non-apoptotic cell death (cytokeratin 18), lactate dehydrogenase release, ATP content and histological analysis. Immunofluorescence was used to quantify proliferative capacity (Ki67) and neuroendocrine differentiation (chromogranin A (LM-NEN)). Metabolic capacity was examined by measuring adenylate energy charge using HPLC. Innate and adaptive immune components of the slices were interrogated using PCR microarray analysis.

Results: Histologically, the characteristic tissue architecture including tumour morphology, stroma and immune infiltration is maintained over the culture period and tissue viability markers remained stable. HCC slices remained viable for up to 8 days and preferred a normoxic environment whereas LM-NEN could be maintained for 15 days when cultured in high oxygen conditions. This was confirmed by consistently low levels of apoptotic cell death (<5%) over duration of culture. Proliferative capacity remained constant and distinctive immunological features associated with an immune infiltrated ('hot')

or immune deserted ('cold') tumour micro-environment were preserved in the slices.
Conclusion: We have successfully developed a human personalised ex-vivo model of primary and secondary liver cancers that retain the structural, metabolic and immunological signatures observed *in vivo*. This model is ideal to understand the immunopathogenesis of liver cancers and could potentially be used to develop a personalised medicine approach for patients to determine best treatments for residual disease post-surgery.

FRI479

Macrophage autophagy protects against hepatocellular carcinoma by modulation of the hepatic immune microenvironment

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Background and Aims: Autophagy is a lysosomal degradation pathway of cellular components that regulates macrophage properties. Macrophages are a major component of leukocyte infiltrate of HCC microenvironment and play a major role in malignant progression by stimulating tumor growth, metastasis, angiogenesis and immune suppression. Here, we investigated the role of macrophage autophagy in hepatocellular development and progression.
Method: Experiments were performed in mice invalidated for the autophagy gene ATG5 in the myeloid lineage ($ATG5^{Mye-/-}$ mice), and their respective littermate wild-type (WT) mice. Hepatocellular carcinoma was induced via a single i.p. injection of N-Diethylnitrosamin (DEN) at day 14. The HCC-related immune response was analyzed by flow cytometry. In vitro, the HCC cell line Hepa1–6 was used in conditioned medium experiments with peritoneal macrophages.
Results: As compared to WT littermates, ATG5Mye−/− mice showed enhanced tumor burden, hepatocyte proliferation and expression of tumoral markers as compared to WT mice. As macrophage autophagy is implicated in the control of immune responses, we evaluated the impact of macrophage autophagy invalidation on the immune microenvironment during hepatocarcinogenesis. By flow cytometry analysis, we showed a significant difference in intrahepatic immune cell populations with a reduction in the number of recruited macrophages, CD4+ T helper cell as well as CD8+ cytotoxic T cell subsets in DEN-treated ATG5Mye−/− mice as compared to treated WT mice. Moreover, recruited macrophages, CD8+ T cells and NK cells exhibited a decrease in activation marker expression suggesting that macrophage autophagy invalidation compromised the antitumor immune response. Finally, *in vitro* studies demonstrated that the conditioned medium of the HCC cell line, Hepa1-6, impaired the autophagy flux of macrophages.
Conclusion: These results demonstrated that macrophage autophagy displays beneficial effects on HCC development and progression by regulating the hepatic immune response. Moreover, our results highlight the existence of a vicious circle in which tumor cells inhibit macrophage autophagy, which in turn suppresses antitumor immune responses leading to tumor progression.

FRI481

Blocking IRE1a-endoribonuclease activity in hepatic stellate cells decreases tumor cell proliferation and metastasis in hepatocellular carcinoma

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Background and Aims: Hepatocellular carcinoma (HCC) is a primary liver tumor that usually occurs in the background of liver cirrhosis. Activated stellate cells play a key role in the pathogenesis of HCC. They are the main source of pro-fibrotic signaling and produce growth factors that actively fuel tumor cell proliferation and migration. In this study, we aimed to identify the role of ER-stress in the cross-talk between stellate cells and cancer cells in HCC.
Method: Mice were injected once per week with diethylnitrosamine to induce HCC with underlying liver cirrhosis. Mice were treated with an IRE1a inhibitor 4u8C or control, samples were taken after 25 weeks. Tumor burden and collagen deposition was quantified on H&E and Sirius red staining, respectively. To study the interactions between stellate cells and tumor cells in vitro, HCC-cell lines (HepG2 and Huh7) and stellate cell line (LX2) were co-cultured using transwell assays, 2D co-cultures, 3D spheroids and cell-engrafted human liver 3D-scaffolds. Chemotaxis was assessed on fluorescently labelled cells using scratch wound assays and 2D CellDirectors, respectively. Images from biopsies from patients with HCC stained with antibodies against WIPI1, SHC1, PPP2R5B and BiP were obtained through the Human Protein Atlas. Gene expression profiles of HCC with and without a fibrous stroma was accessed through PubMed's Gene Expression Omnibus, and a gene-set enrichment assay was performed.
Results: Treatment with 4u8C lead to a significant decrease in size and number of HCC in vivo. Sirius red staining showed a significant decrease in collagen deposition after treatment with 4u8C, compared to controls. In vitro experiments showed that tumor cells secrete factors that cause hepatic stellate cells to undergo endoplasmic reticulum (ER)-stress, which contributes to their activation. These activated stellate cells induce the progression of HCC by promoting tumor cell proliferation and migration. Inhibiting IRE1a-ribonuclease activity with 4u8C or siRNA-transfection decreased stellate cell activation, which inhibited tumor cell proliferation and migration in vitro. A gene-set enrichment assay revealed an increase of genes involved in ER stress in fibrotic samples of HCC patients. Immunohistochemistry on HCC patient-liver biopsies confirmed the presence of ER stress markers in the fibrotic scar tissue and near hepatic blood vessels.
Conclusion: These results suggest that IRE1a could play an important role in mediating the cross-talk between stellate cells and cancer cells. Components of the ER-stress pathway may be therapeutically relevant for treating patients with HCC.

FRI482

Comprehensive analysis of cancer-related genes and AAV/hepatitis B virus integration into genome on development of hepatocellular carcinoma in patients with prior hepatitis B virus infection

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Background and Aims: Hepatitis B viral (HBV) DNA is often integrated into the genomes of hepatocellular carcinoma (HCC) in patients with chronic persistent HBV infection. However, it is controversial whether prior infection of HBV is responsible for hepatocarcinogenesis. This study aimed to elucidate genetic characteristics and viral integration associated with HCC developed from prior infection of HBV.
Method: Two hundred and one HCC patients consisting of 79 non-B non-C (NBNC)-, 79 HCV Ab positive- and 43 HBsAg positive- HCC were investigated. Of these, 21 were prior HBV infection (patients with HBsAg-negative and anti-HBc and/or anti-HBs positive) with

HCV infection, and 30 were prior HBV infection without HCV infection. Genomic DNA obtained from HCC and corresponding background liver were deep-sequenced targeting 54 cancer-related genes. TERT promoter mutation at 2 hot spots, HBV- and AAV-human genomic junction breakpoints were also deep-sequenced on a MiSeq instrument.

Results: In 21 prior HBV with HCV-HCC, recurrent mutations were frequently found in TP53 (9.5%), TERT (85.7%) and CTNNB1 (28.6%), and these gene mutational profile were similar to those in HCV without prior HBV-HCC (TP53 29.3%, TERT 81.0%, CTNNB1 34.5%). However, 30 prior HBV infection without HCV-HCC had substantially different gene mutational profile compared to those in prior HBV with HCV- and HBsAg positive-HCC (prior HBV infection; TP53 46.7%, TERT 70.0%, CTNNB1 33.3%: HBsAg positive; TP53 67.9%, TERT 30.0%, CTNNB1 10.7%: $p < 0.05$). Although 52% background liver of prior HBV with HCV-HCC were diagnosed as cirrhosis, all prior HBV without HCV-HCC were arising from normal liver or chronic hepatitis. In prior HBV without HCV tumor tissue, a total of 21 HBV integration breakpoints were detected in 23.3% (7/30) in 13 cancer-related genes including TERT, MTRNR2L1, NTM which were also targeted by chronic HBV. AAV integration were detected in tumor tissue. Moreover, 7 HBV and AAV2 breakpoints were detected 20% (6/30) in background liver tissue and the virus genome were integrated into cancer-related genes including TERT, PAK5. In contrast to prior HBV without HCV infection, neither HBV nor AAV integration were detected in prior HBV with HCV-HCC.

Conclusion: Half of prior HBV with HCV-HCC were developed from cirrhotic liver and were not related to integration of HBV into human HCC genome. However, prior HBV without HCV-HCC were arising from non-cirrhotic liver and almost 20% had HBV integration into cancer-related genes. These results suggest that prior HBV infection is one of the mechanisms for the development of non HCV-HCC.

FRI484

TIGIT and PD1 dual checkpoint blockade restores functionality of tumor-infiltrating T cells in hepatocellular carcinoma

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Background and Aims: T cell immune receptor with Ig and ITIM domains (TIGIT) has been described as a co-inhibitory receptor on tumor-infiltrating immune cells, and its suitability as a target for cancer immunotherapy is currently being investigated in early-phase clinical trials. For hepatocellular carcinoma (HCC), however, both TIGIT expression and functionality are not yet understood. Here we aim to determine expression of TIGIT, its co-stimulatory counterpart CD226, and their ligand CD155, as well as the effects of TIGIT/PD1 co-blockade in HCC.

Method: Human mononuclear leucocytes were isolated from tumors (TILs), paired tumor free liver tissues (TFL) and peripheral blood of HCC patients, and used for flowcytometric phenotyping and functional assays. Polyclonal and tumor antigen-specific T-cell stimulation assays were used to study the *ex vivo* effects of TIGIT/PD1 single or dual blockade on T cell proliferation.

Results: TIGIT was expressed on cytotoxic T cells, helper T cells and regulatory T cells in tumors as well as in TFL and blood, but tumor-infiltrating T cells showed reduced CD226 expression. Additionally, we found TIGIT was enriched and CD226 expression was reduced in $PD1^{high}$ CD8+ TILs. $PD1^{high}$ TIGIT+ CD8 TILs were found in 53% of HCC patients. They were devoid of perforin and granzyme B, produced lowest IFN-gamma and TNF-alpha in response to PMA/Ionomycin restimulation and had significantly higher TOX expression. Prominent expression of CD155 was found on conventional dendritic cells and monocytes/macrophages, while tumor cells showed significantly higher expression compared to hepatocytes in TFL. Co-blockade of TIGIT and PD1 with specific antibodies improved the *ex vivo* proliferation of CD4+ and CD8+ TILs, especially in low PD1 expressers, but single TIGIT or PD-1 blockade did not. CD226 blockade reversed the effect of TIGIT blockade.

Conclusion: Tumor-infiltrating T cells in HCC show reduced CD226 expression, which may contribute to their suppression via TIGIT within the tumor micro-environment with prominent CD155 expression. TIGIT is enriched in $PD1^{high}$ CD8+ TILs which display a dysfunctional phenotype and express the exhaustion-specific transcription factor TOX. Dual blockade of TIGIT/PD1 increased the *ex vivo* proliferation of CD4+ and CD8+ TILs cells, especially in Low PD1 expressers, suggesting that combined targeting of these two immune checkpoints may have therapeutic promise in about half of HCC patients.

FRI485

Regulation of the biology of cholangiocarcinoma (CCA) cells by the extracellular-signal regulated kinase 5 (ERK5)

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Background and Aims: Cholangiocarcinoma (CCA) is characterized by high resistance to chemotherapy and poor prognosis. Epidermal growth factor (EGF) is involved in CCA development, and over-expression of the EGF receptor (EGFR) has been linked to tumor progression. The EGF signaling pathway may be associated with activation of extracellular signal-regulated kinase 5 (ERK5), a protein belonging to the MAPK family involved in the pathogenesis of different types of cancer. Additionally, ERK5 is implicated in cytoskeletal remodeling and cell motility. The purpose of this study was to investigate the role of ERK5 in the biology of CCA cells.

Method: Two intrahepatic human cholangiocarcinoma cell lines (HuCCT-1 and CCLP-1) and two primary human iCCA cells were used in this study. Cell growth was determined by cell counting and BrdU incorporation assay. Cell motility and invasion were assessed using modified Boyden chambers. ERK5, p-ERK5, EGFR, VEGF and Angiopoietin 1 were investigated by Western blotting. Silencing of cells was performed by gene silencing with shRNA. XMD8-92 and AX15836 were used to inhibit ERK5 activity.

Results: ERK5 was upregulated in all CCA cells examined and phosphorylation of ERK5 was increased in cells exposed to EGF. Growth of CCA cells in serum-containing medium was decreased after exposure to 10μM XMD8-92. In addition, migration and invasion induced by EGF were significantly reduced by both XMD8-92 and AX15836 (2μM). Similar results were obtained in ERK5-silenced cells exposed to EGF, when compared to treated with non-targeting (NT) shRNAs. In addition, in ERK5 silenced cells, expression of VEGF and angiopoietin 1 was reduced compared to NT cells. Of note, conditioned medium (CM) obtained from HuCCT-1 cells induced an increase in migration of both human hepatic stellate cells (HSC) and THP-1 monocytes, an effect reduced when conditioned medium from ERK5-silenced cells was used. Furthermore, the inhibitory effects of metformin on cell growth were more evident in ERK5-silenced cells.

Conclusion: In cholangiocarcinoma cells, ERK5 activity regulates cell growth and motility, release of angiogenic factors and drug resistance.

FRI486

Fatty acids regulate the biology of cholangiocarcinoma cells

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Background and Aims: The incidence of cholangiocarcinoma (CCA) is increasing worldwide and is associated with poor patient outcomes. Identification molecular features of CCA could be helpful in designing new therapeutic approaches. Cancer cells are often exposed to a metabolically challenging environment with scarce availability of nutrients. This metabolic stress leads to changes in the balance between endogenous synthesis and exogenous uptake of fatty acids (FAs), which are needed by cells to support their own growth. Moreover, alterations in lipid metabolism may affect the response of tumor cells to different drugs. Yet, little is known about the lipid profile of CCA.
Method: CCA cells lines (CCLP1, HUCCT) were treated with increasing concentration of different fatty acids for 48 h, and cell viability was evaluated. Proliferation and survival were evaluated with Western Blot analysis. Responsiveness of CCA cells to Oxalyplatin, Cisplatin and 5-FU was tested with crystal violet staining. The epithelial-mesenchymal transition program and stem-like markers were tested with real-time PCR.
Results: Exposure of both CCA lines to fatty acids led to a marked increase in cell proliferation, especially with oleic and palmitoleic acid. Western blot analysis demonstrated a robust activation of growth and survival pathways, including AKT and ERK1/2. In addition, exposure to fatty acids before treatment with and chemotherapeutic agents made CCA cells less sensitive to the toxic action of these drugs. Finally. Fatty acid treatment resulted in a marked upregulation of genes controlling epithelial-mesenchymal transition and key gene controlling stemness.
Conclusion: Our results indicate that CCA cells exploit lipid metabolism to gain growth, invasiveness and survival advantages. When exposed to fatty acids, cancer cells are more resistant to the toxic effects of antineoplastic drugs, show a modulation of stem-like features, indicating that lipid metabolism could be a new potential target to affect CCA progression.

FRI487

Circulating exosomal microRNA-125b inhibits metastasis of hepatocellular carcinoma

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Background and Aims: Exosomes are 30–150 nm-sized vesicles that are released from many cell types into the body fluids. Exosomal miRNAs have recently emerged as potentially promising biomarkers in cancers and play an important role in cell to cell communication. The aim of this study is to investigate exosomal miRNAs regulating extrahepatic metastasis from hepatocellular carcinoma (HCC).
Method: Microarray-based miRNA profiling was performed to explore potential markers on the whole blood samples from patients with various liver diseases. Exosomes were extracted using Exoquick and Total exosome isolation kit (TEI), respectively. The selected miRNAs were tested in sera of 45 healthy controls and 239 patients with and without metastasis. Then, target gene prediction was performed using TargetScan. Targets by miRNAs and epithelial-mesenchymal transition (EMT)-related protein expressions were assessed by Western blot. Transfer of miRNA through exosome into recipient cells was confirmed by confocal microscopy. Biological functions of selected exosomal miRNAs in metastasis were investigated with a series of in vitro experiments including cell migration and invasion assay.
Results: Microarray-based miRNA profiling revealed several miRNAs with differential expressions, of which four exosomal miRNAs were further evaluated regarding metastasis. Transmission electron microscopy and western blot assay for exosomal markers confirmed the isolation of circulating exosomes from serum and cell conditioned media. Among the selected miRNAs, exosomal miR-125b correlated with patient outcome, with increasing expression trends with tumor stage progression but followed by a significant drop with extrahepatic metastasis. Low exosomal miR-125b expression was associated with poor survival in patients as well as early metastases. For patients with serial serum samples before and after metastasis, exosomal miR-125b levels decreased upon metastasis. The miRNA was taken up into recipient cells through exosome transfer. Transfection of exosome with miR-125b mimic downregulated SMAD2 expression level of recipient cells to regulate cancer metastasis. Moreover, miR-125b mimic inhibited migration and invasion ability of recipient cells.
Conclusion: Exosomal miR-125b has an anti-metastatic role by inhibiting metastatic ability and regulating EMT in HCC. Our findings suggest that exosomal miR-125b could be a potential biomarker and novel therapeutic target for metastasis from HCC.

FRI488

Modelling liver tumor organoids and cancer-associated fibroblasts interaction reveals the robust effects of stromal niche in cancer nurturing and treatment resistance

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Background and Aims: Cancer associated fibroblasts (CAFs) are known to play a key role in a variety of cancer types. However, there is a lack of robust models for studying the interactions between liver cancer cells and CAFs. We aim to establish a 3D organotypic co-culture model of primary liver tumor derived organoids with CAFs, and to understand their interactions and the response to treatment.
Method: Mouse liver tumor organoids and CAFs were cultured from N-nitrosodiethylamine induced mouse tumors. Human tumor organoids were from primary cholangiocarcinoma (CCA) and CAFs derived from hepatocellular carcinoma (HCC) or CCA. Liver tumor organoids and CAFs were sorted out by using flow cytometry and then co-cultured to establish a 3D co-culture model in vitro. This co-culture model and a trans-well culture system were used to study the direct contact or paracrine effect in cell proliferation and relative gene expression. Xenograft model was used to interrogate the cell-cell interactions *in vivo*. The effects of CAFs or its conditioned medium on the response of tumor organoids to anti-HCC drugs were tested.
Results: We observed that the expression of several CAFs markers, including FAP, CD29 and Periostin was significantly elevated in tumor compared to adjacent tissues in our HCC cohort ($n = 75$, $p < 0.001$). This was further confirmed in the publically available TCGA database, and importantly high level expression of FAP, CD29 or Periostin was correlated with poor overall survival of liver cancer patients ($p < 0.05$, $n = 36$ CCA and 364 HCC). To functionally investigate the interactions of liver tumor cells with CAFs, we have successfully established 3D co-culture models of liver tumor organoids with CAFs of mouse or human origin. We found that CAFs promote tumor organoid growth ($n = 18$, $p < 0.01$) but not initiation in co-culture with direct cell-cell contacts. However, this effect is also partially through paracrine signaling as demonstrated in the trans-well system ($n = 6$, $p < 0.01$). Reversely, the conditioned medium from organoids also enhances the proliferation of CAFs and regulates CAF markers expression ($n = 6$, $p < 0.01$). Consistently, co-transplantation of CAFs with liver tumor

organoids of mouse (n = 9, p < 0.05) or human (n = 5, p < 0.01) origin promotes tumor growth in xenograft models *in vivo*. Moreover, organoids conferred resistance to clinically used anti-HCC drugs Sorafenib and Regorafenib in the presence of CAFs (n = 6, p < 0.001), or the conditioned medium of pre-treated CAFs (n = 6, p < 0.05).

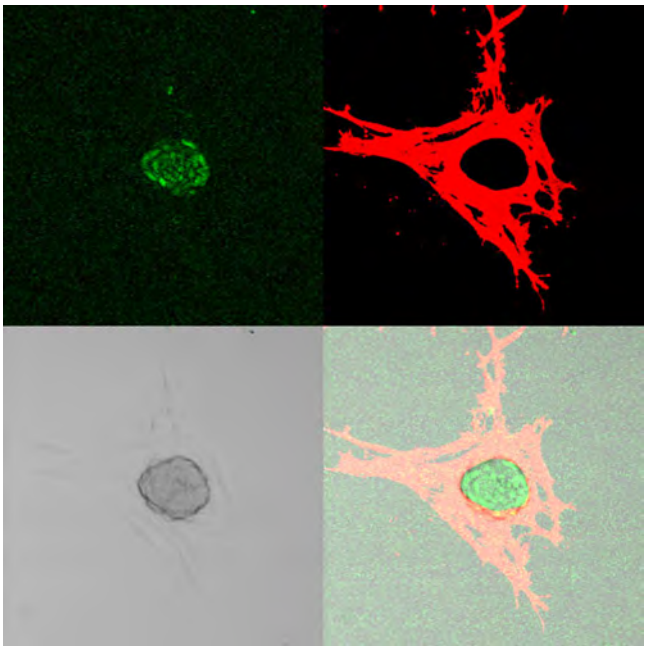

Figure: (abstract: FRI488)

Conclusion: We have successfully established 3D co-culture models of primary liver tumor derived organoids with CAFs of mouse or human origin. We have revealed the robust effects of CAFs in liver cancer nurturing and treatment resistance. These model systems will be helpful for future research on the interactions of liver cancer cells with the stromal compartment and facilitate therapeutic development.

FRI490

ZEB1 promotes cholangiocarcinoma progression through tumor dedifferentiation and paracrine signaling between tumor cells and cancer-associated fibroblasts

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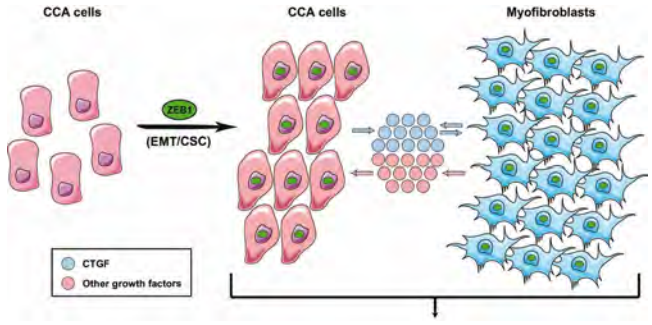
Background and Aims: Cholangiocarcinoma (CCA) arises from biliary epithelial cells and has poor prognosis due to its late clinical presentation and the lack of effective non-surgical treatment. CCA is characterized by a prominent fibrous stroma mainly composed of cancer-associated fibroblasts (CAF). ZEB1 is a transcription factor expressed by tumor and stromal cells including CAF that contributes to the acquisition of metastatic and stem cell properties. Recently, ZEB1 has been associated with poor prognosis in CCA. Yet, the regulatory functions that ZEB1 exerts in CCA are poorly defined.
Method: Correlations of ZEB1 expression with selected markers in human CCA, were investigated by transcriptomic analyses of whole tumor or laser microdissected stroma and by immunohistochemistry. Viral infection was used to generate gain/loss of function models in human CCA cell lines and liver myofibroblasts (LMF), i.e. immortalized activated hepatic stellate cells, as a model of CAF. Conditioned media (CM) was used to examine tumor-stroma communication. In vivo experiments were performed using a xenograft tumor model in immunodeficient mice.



Results: ZEB1 was expressed in tumor cells in 20% of human CCA and its expression was associated with poor differentiated tumors (p < 0.05). In vitro, ZEB1 promoted the acquisition of EMT/CSC traits in tumor cells along with increased migration and spheroid formation. In vivo, CCA cells that expressed ZEB1 formed larger tumors with higher stromal content. Interestingly, we found an increased expression of the fibrotic marker CTGF in tumor cells and in human and mouse CCA that correlated with ZEB1 expression, suggesting a role of CTGF in the development of desmoplastic microenvironment. In vitro, CM from CCA tumor cells overexpressing ZEB1 or CTGF induced LMF proliferation. Moreover, ZEB1 was found to be expressed by alpha-SMA positive CAF in human CCA. At mRNA level, ZEB1 correlated with alpha-SMA, COL4A1, TGF-beta and CTGF in LMF and in human and mouse CCA stroma. Co-injection of tumor cells plus ZEB1-expressing LMF generated larger tumors than tumor cells plus ZEB1-invalidated LMF. Crosstalk experiments showed that CM from ZEB1-expressing LMF increased tumor cell viability as compared to CM from ZEB1-invalidated LMF.
Conclusion: ZEB1 plays a key role in CCA progression by regulating tumor cell-LMF cross-communication, leading to tumor dedifferentiation and CAF activation.

FRI492

DNA damage response protein checkpoint kinase 2 (CHK2) links chromosomal instability to cellular metabolism in hepatocellular carcinoma (HCC)

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Background and Aims: Chromosome mis-segregation can cause DNA damage and induce DNA damage response (DDR). Although known as an energy-dependent process, mechanisms linking DDR to HCC cellular metabolism are unknown. Here, the involvement of CHK2, a central effector of DDR, in energy expenditure, mitochondrial functions and glycolysis was investigated.
Method: Extracellular vesicles-associated total mRNA was extracted from blood of patients with HCC (n = 22), cirrhosis(n = 14)and 20 healthy subjects. Steady-state metabolomic profile was performed by 1H-NMR spectroscopy in patients and cell cultures. Expression of pyruvate kinase M2 (PKM2), succinate dehydrogenase (SDH), CHK2 and γ-H2AX was evaluated by IHC in a HCC transgenic model. HuS, a human hepatocyte cell line immortalized with TERT, Huh7 and colon carcinoma cell line HCT116 were used and Illumina RNAseq was performed. Glycolysis and O2 consumption was quantified by Seahorse XF-96 analyser. Intracellular ATP was quantified by FRET-based biosensor and quantification of glycolytic/TCA cycle intermediates by trace experiments. Mitochondrial functions were assessed by TMRM.
Results: HCC patients have increased CHK2 mRNA content in extracellular vesicles which was associated with increased glycolytic metabolites. This was confirmed in a transgenic HCC model with elevated expression of PKM2 and SDH in neoplastic lesions associated with a nuclear upregulation of γ-H2AX/CHK2. During mitosis, PKM2 and phosphoglycerate kinase 1 co-localize with CHK2 and CHK2 controlled PKM2 and SDHA expression, whilst intervening with mitochondrial functions confirmed by SDH-dependent ROS production RNAseq data provided significant changes in metabolic pathways. Cells with high levels of γ-H2AX and CHK2 exhibited increased extracellular acidification-and O2 consumption rate. Unstable cells significantly rely on glycolysis for ATP production due to a defective function in mitochondrial ATP production; abolished by CHK2 knockdown. CHK2 and γ-H2AX expression promote glycolysis and succinate oxidation in unstable cells marked by increased glucose oxidation through the TCA cycle. Mitochondrial TMRM fluorescence confirmed that CHK2-controlled SDH expression is key in sustaining $\Delta\psi$m hyperpolarization and ROS production.
Conclusion: These data demonstrate that DNA damage and CHK2 exert an unprecedented recognized control of mitochondrial function and indicate that CHK2 is a pivotal mediator in linking DDR to cellular metabolism and mitochondrial functions.

FRI493

Interplay of PNPLA and HSD17B13 variants in modulating the risk of hepatocellular carcinoma among hepatitis C virus infected patients

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Background and Aims: A single nucleotide polymorphism causing a C to G change in the PNPLA3 gene (rs738409) is associated with disease severity and development of hepatocellular carcinoma (HCC) in non-alcoholic fatty liver disease; the insertion variant rs72613567: TA of the 17β-Hydroxysteroid-dehydrogenase type 13 (HSD17B13) mitigates this detrimental effect. Our aim was to evaluate if the same holds true in chronic hepatitis C virus infection (HCV).
Method: With a case control retrospective study design, we selected 110 patients who developed HCC on a background of HCV infection, matching each HCC patient for sex and age (±30 months) to three HCV infected, non-HCC patients. All participants underwent genotyping for *PNPLA3* and *HSD17B13*) gene variants. Both univariate and multivariate (conditional logistic regression) analysis of risk factors for advanced disease and HCC were performed.
Results: Carriage of *PNPLA3* G* allele was associated with a trend of progressively more severe liver disease, from mild fibrosis to significant fibrosis, cirrhosis and HCC (p = 0.007). When the *HSD17B13:TA* status of these patients was taken into account, the abovementioned trend was strengthened among *HSD17B13* wild-type homozygotes, and completely blunted among carriers of the variant allele (p = 0.0003 and 0.953, respectively) (Figure, panels A and B).
In a conditional logistic regression model including diabetes and AST-to-platelets ratio index in the set of predictor variables, the unfavourable genetic profile characterized by the co-existence of mutated *PNPLA3* and *HSD17B13* wildtype was an independent risk factor for HCC (OR = 2.00, CI95%: 1.23–3.26) together with history of alcohol abuse.
Conclusion: The combination of being *PNPLA3* mutated and *HSD17B13* wild-type significantly increases the risk of developing HCC among HCV-infected patients. The interplay between the two genes may explain some of the controversy on this topic, and may be exploited to stratify HCC risk in hepatitis C.

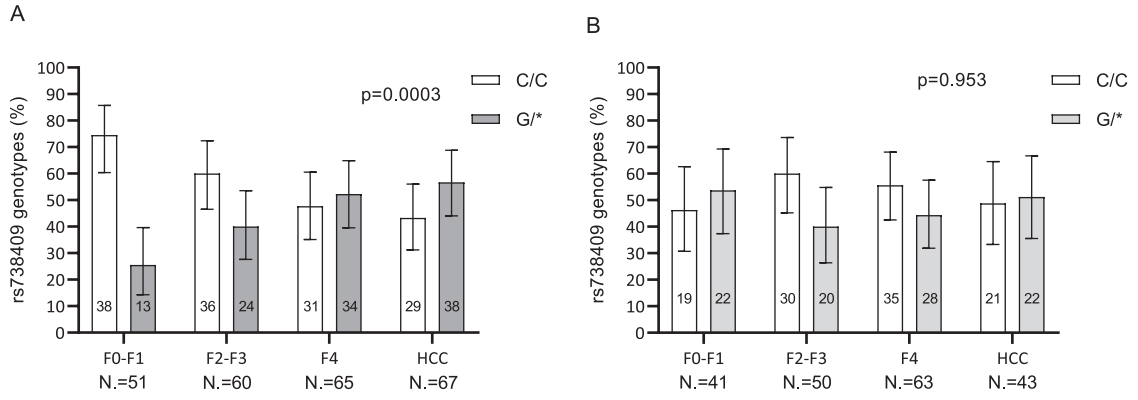

Figure: (abstract: FRI493)

FRI494

Alisporivir, a cyclophilin inhibitor, reduces fibrosis and tumor burden derived from non-alcoholic steatohepatitis in a mouse model

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Background and Aims: With the rise of obesity and diabetes, non-alcoholic fatty liver disease has become the most prevalent liver disorder in the Western world. Accumulation of fat droplets in hepatocytes creates stress in the liver and can progress to non-alcoholic steatohepatitis (NASH) and fibrosis. Patients with NASH are at increased risk to advance to hepatocellular carcinoma (HCC), one of the major causes of cancer mortality. With limited approved efficient treatment for HCC and none for NASH, we aimed to examine whether alisporivir (ALV), a non-immunosuppressive cyclophilin inhibitor, would decrease the development of fibrosis and HCC from NASH in a mouse model.
Method: Male C57BL/6J mice were administered 0.2 mg streptozotocin at 2-day-old to disrupt pancreatic cells and nourished with high-fat diet (60%kcal fat) since 3-week-old. Mice were then randomly assigned to be orally treated with 50 mg/kg ALV (n = 10) or vehicle control (n = 6) daily for 10 weeks before the 30-week-old endpoint for the establishment of HCC. Body weight and liver weight were recorded. Moreover, livers were histologically examined for inflammation, steatosis, and ballooned cells. Collagen was measured by Sirius Red staining of hepatic tissues. Nodules of livers were measured and scored according to a developed system with number and size of nodules as criteria. Two-tailed Mann-Whitney statistical analyses, with alpha value set at 0.05, were conducted with GraphPad Prism.
Results: Decreased body weight (p = 0.0596) and liver weight (p = 0.0397) were observed in ALV-treated mice compared to vehicle control. However, steatosis and ballooning were evident in both murine groups (p > 0.9999). In contrast, ALV reduced collagen deposition (p = 0.0420) and inflammation score (p = 0.0396). Moreover, ALV statistically reduced the number of tumorous nodules (p = 0.0075) and tumor burden (p = 0.0246). No evidence of toxicity was observed.
Conclusion: Our study suggests ALV as a safe and potent candidate for clinical trials on both NASH-derived fibrosis and HCC. Future studies include determining the mechanisms of action of ALV on decreasing tumorous nodule formation and comparing the efficacy of ALV to other cyclophilin inhibitors.

FRI495

2-deoxy-D-glucose encapsulated PLGA nanoparticles suppress hepatocellular carcinoma through cytotoxic effect and activation of antitumor immunity

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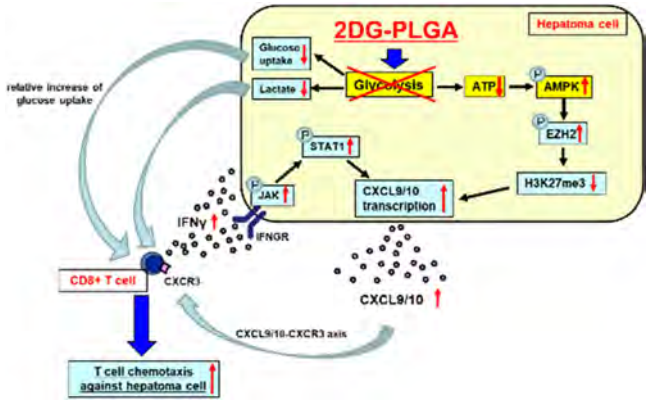
Background and Aims: The glucose derivative, 2-deoxy-D-glucose (2DG) has been shown to exert antitumor effect through inhibition of anaerobic glycolysis. We have developed 2-deoxy-D-glucose (2DG)-encapsulated poly (lactic-co-glycolic acid) (PLGA) nanoparticles as a cancer cell-specific inhibitor of glycolysis.
Method: We investigated whether 2DG-PLGA exerts antitumor effect on HCC, using hepatoma cell lines, nude mice with xenograft tumors, and hepatocarcinogenic mouse model.
Results: In vitro 2DG inhibited cell proliferation and induced apoptosis through the suppression of anaerobic glycolysis, ROS production and activation of ER stress. The in vivo imaging system combined with PLGA encapsulating the fluorescent dye ICG demonstrated specific accumulation of PLGA in HCC xenograft tumor. Of note 2DG-PLGA exhibited more vigorous antitumor effect along with CD3 and IFN-γ-positive lymphocyte infiltration into HCC in immunocompetent mice (STAMTM mouse and DEN-induced HCC mouse models) without any adverse effects. The following results were obtained as the underlying mechanisms behind activation of tumor immunity by 2DG-PLGA. 2DG-PLGA increased the production of chemokines (CXCL9 and 10) through the activation of IFN-γ/Jak-Stat1 signal and the inhibition of histone methylation via AMPK activation. Glucose uptake decreased in Huh7 cells but increased in T-cells after co-culture of both cells following 2DG treatment, which promoted chemotaxis of T-cells ex vivo. The infiltration of regulatory T-cells was not increased by 2DG-PLGA in immunocompetent mice. We also found that 2DG-PLGA exhibited antitumor effect in C57BL/6 mice transplanted with PD1-resistant melanoma cell line (B16F10). Furthermore, combined administration of 2DG-PLGA and PD-1 antibody therapy markedly exhibited antitumor effect in STAMTM mice. Finally, metabolome analysis revealed that 2DG did not compensate activation of fatty acid synthesis under circumstances of glycolysis suppression.



Conclusion: The 2DG-PLGA specifically inhibited cancer cell glycolysis, and suppressed HCC development through cytotoxic effect and activation of antitumor immunity. These results show the promising potential of 2DG-PLGA as a new therapeutic agent against HCC.

FRI496

SPARC negatively correlates with prognosis after transarterial chemoembolization and facilitates growth and metastasis of hepatocellular carcinoma via ERK/MMP signaling pathways

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Background and Aims: Transarterial chemoembolization (TACE) represents a widely accepted treatment procedure for intermediate stage or unresectable hepatocellular carcinoma (HCC). Nevertheless, the prognosis associated with TACE remains poor. Extrahepatic progression following TACE is an important factor in this context. However, very few studies have evaluated serologic prognostic factors in HCC patients before TACE. Secreted protein acidic and rich in cysteine (SPARC) is a matricellular glycoprotein that can remarkably affect tumorigenesis and metastasis, leading to the poor prognosis in HCC. Therefore, for further exploration of the potential value of SPARC in preoperative prognosis of HCC patients undergoing TACE, the expression of SPARC in patient sera was quantified. Furthermore, the molecular mechanisms underlying the regulation of HCC by SPARC were investigated.
Method: The study population included 43 HCC patients who underwent TACE. We collected and analyzed information on their clinical characteristics and survival. To evaluate SPARC expression in

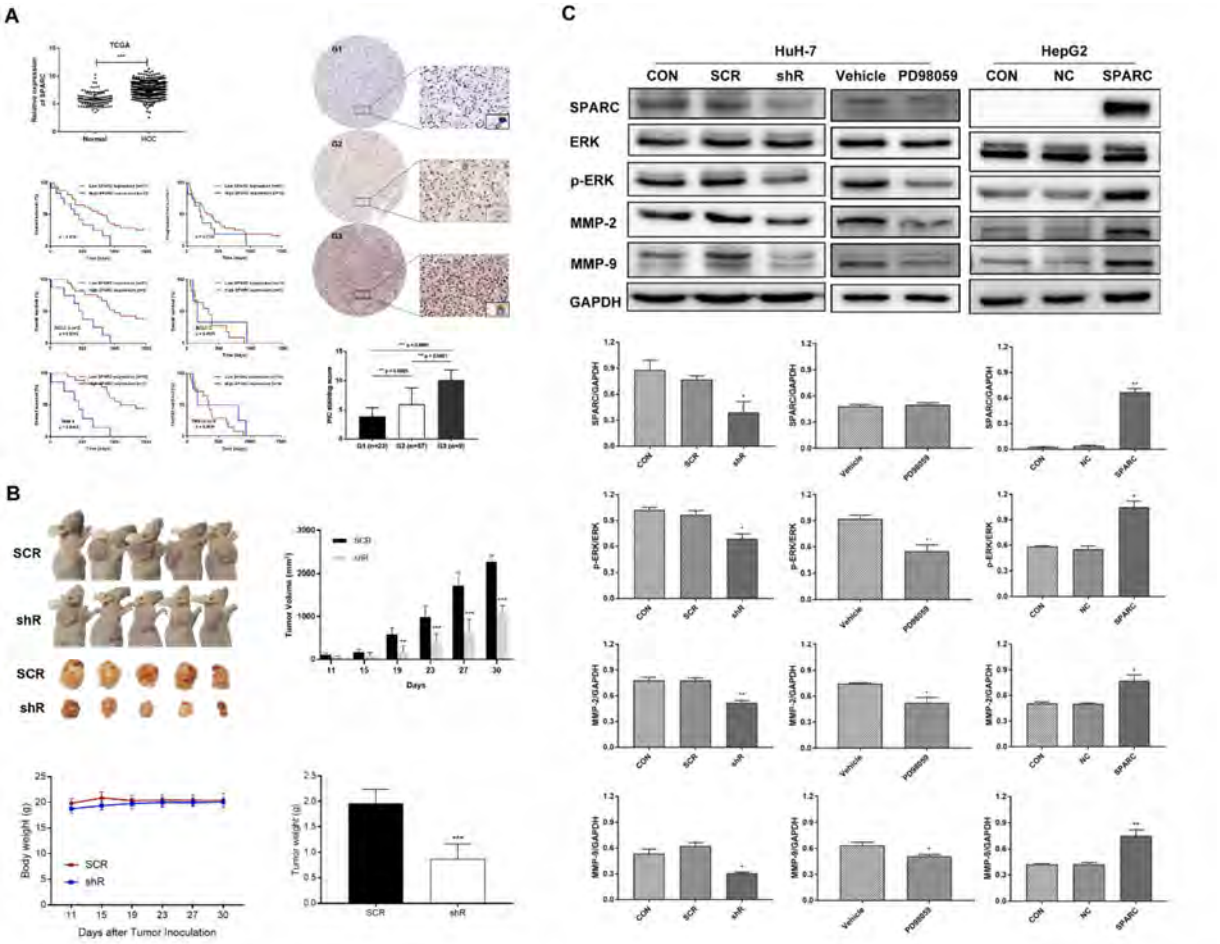

Figure. Serum expression of SPARC in HCC patients treated with TACE was related to the overall survival time. SPARC was significantly upregulated in high pathological grade human HCC tissues (A). SPARC downregulation inhibits tumor growth in vivo (B). Knockdown of SPARC inhibits the ERK1/2-MMP2/9 pathway, leading to suppression of HCC cell proliferation and metastasis (C). *p < 0.05, **p < 0.01, and ***p < 0.001.

different pathological tissue grades, we studied tissues collected from 89 HCC patients by immunohistochemical assays. We designed lentiviral vector plasmids that carried interference sequences as well as plasmids that harbored the complete open reading frame of SPARC for the knockdown or overexpression of SPARC in HuH-7 or HepG2 cells, respectively. This allowed us to determine the biological functions of SPARC in vitro and in vivo. In addition, the expression levels of extracellular signal-regulated kinases 1/2 (ERK1/2) and matrix metalloproteinases 2/9 (MMP2/9) were evaluated.

Results: We evaluated the association of serum SPARC levels with survival at different TNM and Barcelona-Clinic Liver Cancer (BCLC) stages in HCC patients treated with TACE. We observed a significant upregulation of SPARC in high pathological grade human HCC tissues, which predicts unfavorable prognosis and suggests an important tumor-promoting effect of SPARC. Functional studies indicate that downregulation of SPARC expression contributed immensely to the inhibition of HuH-7 cell proliferation and metastasis in vitro, whereas the overexpression of SPARC leads to opposite phenotypes. Mechanistically, decreased SPARC expression results in dephosphorylation of ERK1/2 and deactivation of MMP2/9, thereby inhibiting HCC growth and metastasis. Importantly, low expression levels of SPARC inhibited the formation of subcutaneous tumors in nude mice.

Conclusion: SPARC was found to facilitate HCC proliferation and metastasis via modulation of the ERK1/2-MMP2/9 signaling pathways. Our research elucidates the biological mechanism of action of SPARC and may contribute to the treatment of liver cancer.

FRI497

Patient-derived ECM-scaffolds of colorectal cancer and liver metastases as organotypic 3D model of liver metastatic colonization

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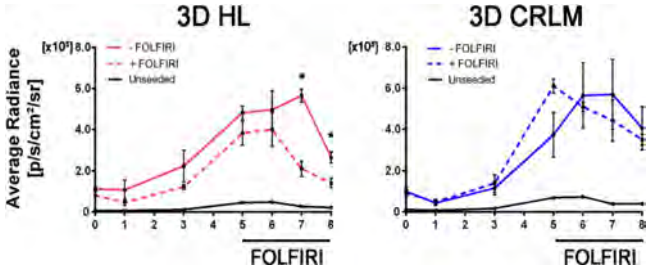
Background and Aims: Colorectal cancer (CRC) is the second leading cause of cancer-related deaths, and liver is the most common site of CRC metastasis. None of the current tissue culture models for studying hepatic metastasis mimics the biological, biochemical and structural characteristics of the metastatic microenvironment such as the extracellular matrix (ECM). The aim of this study was to develop a 3D model of colorectal cancer liver metastasis (CRLM) and matched CRC using patient-derived decellularized matrices to recapitulate and study the role of the tissue-specific microenvironment.
Methods: Decellularization of patient-derived samples of matched healthy colon (HC), CRC, healthy liver (HL) and CRLM was performed with a detergent-enzymatic process. A 3D culture model was generated seeding decellularized scaffolds with CRC cell line HT-29.



Results: Decellularization preserved tissue-specific biological and ultrastructural properties of CRC and CRLM ECM. Seeded CRLM and CRC scaffolds supported cancer cell adhesion and, when compared to the respective normal counterpart, they showed increased proliferation and migration. 3D models generated with CRC and CRLM scaffolds also demonstrated induction of epithelial-mesenchymal transition (EMT), supported by protein expression (E-cadherin, Vimentin and SNAI1/2) and gene set enrichment analysis. Cells cultured in the CRLM environment displayed significant differences in their gene expression profile in respect to conventional 2D cultures, with the most represented biological processes involving cellular response to stress metabolic processes, to oxygen level and to starvation, and demethylation and deacethylation. When HT-29 cells grown in CRLM or HL scaffolds were exposed to IC_{50} of 5-FU and FOLFIRI determined in 2D conditions, the cellular response to the chemotherapy agents was affected by the tissue-specific decellularized scaffolds. HT-29 cells grown in CRLM scaffolds, but not in HL scaffolds, were more resistant to treatment with 5-FU and FOLFIRI (Figure), which would be the normal situation in man.
Conclusion: We have established a physiologically relevant 3D tissue culture model which is able to mimic in vivo features of CRLM such as proliferation, migration, and chemotherapeutic drug response of CRC cells in liver metastatic tissue and, as such, represents a new powerful tool to investigate formation and progression of liver metastases.

FRI498

Interplay between O-GlcNAc transferase and enhancer of zeste homolog 2 in hepatocellular carcinoma

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Background and Aims: Hepatocellular carcinoma (HCC) is the second leading and fastest rising cause of cancer death worldwide. Despite recent improvements, treatment options for HCC remain largely unsatisfactory. Increased expression of histone methyltransferase enhancer of zeste homolog 2 (Ezh2), responsible for H3K27 di- and trimethylation (H3K27me2 and H3K27me3), is frequently detected in HCC tissues and correlates with the aggressiveness and/or poor prognosis of HCCs. Ezh2 knockdown in HCC cells reverses tumorigenicity in a nude mouse model, suggesting a potential therapeutic value of Ezh2 inhibition in HCC. Ezh2 activity is regulated by post-translational modifications, including phosphorylation and glycosylation by O-linked N-acetylglucosamine (O-GlcNAc) transferase (OGT). We have previously shown that OGT expression is increased in tumor tissue from HCC patients (Herzog et al. Gut 2019). In breast cancer MCF-7 cells, OGT and Ezh2 have been reported to co-repress a subset of potential tumor suppressor genes. The aim of our project is to uncover the interplay between OGT and Ezh2 in HCC.
Method: Liver tissues samples from HCC patients were analyzed by RT-PCR. O-GlcNAcylated proteins were purified using a click chemistry-based protocol. Multiplex transcriptomic analysis of human hepatoma HepG2 cells was performed using NanoString nCounter® technology. Chromatin immunoprecipitation (ChIP) PCR experiments were done using antibodies directed against OGT, Ezh2 or H3K27m3.
Results: We showed that in a cohort of 183 HCC patients, OGT and Ezh2 are upregulated in tumor tissue as compared to peri-tumor tissue. Analysis of purified O-GlcNAcylated proteins showed that Ezh2 is post-translationally modified by OGT in HepG2 cells. Transcriptomic analysis of HepG2 cells showed that OGT- and Ezh2-silencing modulate the expression of more than 100 genes belonging to major different cancer-associated canonical pathways. ChIP experiments demonstrated that OGT and Ezh2 are recruited to the promoter region of several genes whose expression increased following silencing of either OGT or Ezh2 and marked by H3K27m3, suggesting that these genes are targeted for repression by OGT and Ezh2 in transformed liver cells.
Conclusion: Taken together, our data uncovered an interplay between OGT and Ezh2 associated with the modulation of cancer pathways in transformed liver cells and provides perspectives for epigenetic strategies as potential future anti-HCC therapies.

FRI499

The metabolic plasticity of neoplastic cholangiocytes: perspective for target therapy in intrahepatic cholangiocarcinoma.

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Background and Aims: Intrahepatic cholangiocarcinoma (iCCA) is a deadly cancer arising from biliary epithelial cells (BECs) lining the biliary tree. iCCA is a highly chemoresistant tumor and pharmacological therapies are generally unsuccessful. Furthermore, due to the

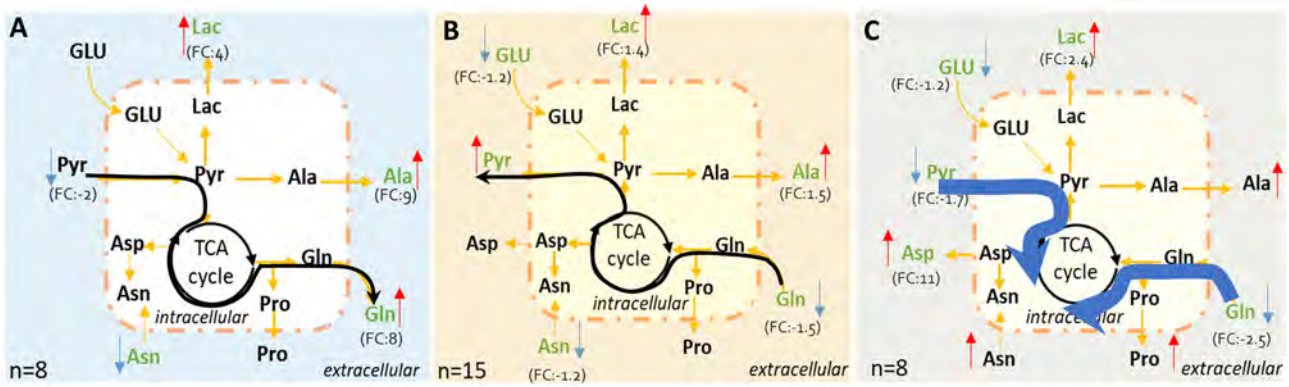

Figure 1: (abstract: FRI499): A) Metabolic pathway of primary BECs cultured with Human Cholangiocyte Medium (Celprogen); B) Metabolic pathway of iCCA cells; As shown, GLUTAMINE and PYRUVATE are metabolic sources that fuel central metabolism for both kind of cells. C) iCCA cells cultured with Human Cholangiocyte Medium highlighted their metabolic plasticity: iCCA cells used PYRUVATE when it was present in the medium.

complexity of the in vivo cellular interactions, metabolic activation pathways are largely unknown. We herein aim to elucidate the metabolic asset of both tumoral and non-tumoral primary BECs by profiling both the extra- and endo- metabolome.
Method: Primary non-tumoral BECS (NT-BECs) and tumoral iCCA BECs (iCCA-BECs) were isolated from 15 patients surgically resected at the Division of Hepatobiliary and General Surgery, Humanitas Clinical and Research Center. Both tumoral and non-affected BECs from the same donor were cultured until reaching 80% of confluence. Cells and their conditioned medium were analyzed by using mass spectrometry-based untargeted and targeted metabolomic approaches to explore the main metabolic processes. Moreover, primary iCCA BECs and Hucc-T1, human iCCA immortalized cell line, were seeded in 96-well plates to perform proliferation assay at different time point with different culture medium to detail the involvement of nutrients in iCCA-BEC proliferation.
Results: We observed that iCCA-BECs were characterized by higher mitochondrial activity compared to NT-BECs in all samples, in which glutamine and pyruvate act as metabolic sources to fuel central metabolism respectively. Importantly, iCCA-BECs exposed to different nutrient environments were able to reprogram nutrient uptake and utilization to boost central cellular metabolism. Furthermore, the proliferation assay showed that iCCA-BECs, when cultured in a different metabolic medium composition, were able to exploit the different metabolic sources to sustain cancer cell growth.
Conclusion: This observation raises the prospect that interfering with mitochondrial activity of iCCA cancer cells could make them more susceptible to cytotoxic drugs, opening new possibility to improve the outcomes of the iCCA patients.

FRI500

Mitochondrial oxidative metabolism contributes to maintain a cancer stem cell phenotype in cholangiocarcinoma

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Background and Aims: Accumulating evidence indicates cancer stem cells (CSC) as a key target in cancer. Although metabolic reprogramming is considered an important feature of cancer cells, little is known about metabolic regulation in CSC derived from cholangiocarcinoma (CCA). This study investigated the role of mitochondria-dependent metabolism and of the related signaling pathways in the maintenance of a stem-state in CCA.
Method: Stem-like subset was enriched by sphere culture (SPH) in established human intrahepatic CCA cells (HUCCT1, CCLP1). Extracellular flux analysis was examined by Seahorse technology. Mitochondrial membrane potential and mitochondrial mass were assessed by MitoTracker Red and MitoTracker Green, respectively. Glucose uptake was quantified by incorporation of (U-14C)-D-Glucose. Gene set enrichment analysis (GSEA) and correlation with overall survival (OS) (log rank/Mantel-cox statistics) and time to recurrence (TTR) (Gehan-Breslow Wilcoxon test) were carried out from a transcriptome database of 104 CCA patients.
Results: In contrast to parental cells grown as adherent monolayers (MON), metabolic analyses by Seahorse revealed a more efficient respiratory phenotype in CCA-SPH, due to mitochondrial oxidative phosphorylation. In addition, CCA-SPH retained high mitochondrial membrane potential and elevated mitochondrial mass, as well as over-expression of PGC-1α, a master regulator of mitochondrial biogenesis. In vitro targeting of mitochondrial complex I by metformin impaired the ability to form SPH, expression of CSC-associated genes, and genes related to pluripotency and epithelial mesenchymal transition. In an in vivo model in immunocompromised mice, growth of tumors derived from CCA-SPH was suppressed by metformin. Furthermore, PGC-1α silencing highly reduced the expression of stem-like markers in CCA-SPH, and reduced sphere-formation and cell invasion. Notably, GSEA analysis showed that patients with with high levels of mitochondrial complex II had a worse prognosis in terms of OS ($p = 0.036$) and TTR ($p = 0.029$). In addition, PGC-1α was significantly correlated with mitochondrial complex II and stem-like genes in CCA patients.
Conclusion: Our data indicate a pivotal role of mitochondrial oxidative metabolism in the biology of the stem-like subset in CCA.

FRI502

NEDD8 specific protease 1 (NEDP1) as a tumor suppressor in hepatocellular carcinoma

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Background and Aims: Neddylation is a reversible posttranslational modification similar to ubiquitination that conjugates to target

proteins promoting their stabilization. NEDDylation is implicated in the regulation of almost every biological process. Liver cancer is the sixth most common cancer diagnosed and the fifth with the highest mortality worldwide in 2018, being hepatocellular carcinoma (HCC) the most common subtype. Due to the high mortality of HCC rate and the lack of effective, new strategies must be developed. Neddylation levels increase in HCC and correlated with those patients with a worse prognosis. Therefore, understanding the molecular basis for the observed defects in protein NEDDylation in tumors will not only assist the use of NEDD8 inhibitors in the clinic but could also potentially identify new therapeutic targets within the NEDD8 pathway. In this context emerges NEDD8 specific protease 1 (NEDP1), a protease that processes NEDD8 and catalyzes the de-neddylation of substrates. Therefore, the potential deregulation of this protease (NEDP1) will be evaluated in liver cancer patients.
Method: Preclinical animal models of liver cancer as well as human hepatocytes and hepatoma cells have been used in this study.
Results: NEDP1 levels are significantly reduced in mice model liver tumours, correlated with the increase in hepatic global Neddylation in comparison with a healthy liver. Interestingly, Senp8 (NEDP1 gene) does not show any transcriptional regulation suggesting posttranslational mechanisms underlying this modulation. Likewise, levels of NEDP1 in human liver cancer cell lines decrease, accordingly with increases in protein neddylation. In C elegans and human cells, NEDP1 induction upon DNA damage converts NEDD8 poly-chains (K11/K48) into mono-NEDD8. This promotes the activation of HSP70, which subsequently allows the oligomerization of APAF1 into the apoptosome, inducing apoptosis. More studies are required to understand the role of NEDP1 in HCC.
Conclusion: NEDP1 could act as a tumor suppressor in liver cancer.

FRI503
Piddosome-controlled liver ploidy is predictive for HCC outcome
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Background and Aims: PIDDosome is a multiprotein complex involved in regulation of hepatocyte ploidy by caspase-2-mediated MDM2 cleavage followed by p53 stabilization and cell cycle arrest. Here, we aimed to investigate the role of the PIDDosome in hepatocellular carcinoma (HCC) using animal models combined with analysis of human patient samples.
Method: HCC was induced by intraperitoneal DEN injection in wild type animals (*wt*) as well as in mice deficient in one of the three PIDDosome proteins CASP2, RAIDD/CRADD or PIDD1. Tumor load was assessed 10 months after DEN injections. Hepatic ploidy was evaluated by DNA staining and flow cytometry, morphometric analysis and bulk sequencing. Proliferation was assessed by Ki-67. Public TCGA expression data sets were interrogated to correlate mRNA tumor levels of *CASP2, RAIDD* and *PIDD1* with proliferation, survival as well as with disease stage of HCC patients. Moreover, morphometric assessment of nuclear size and spatial density as a surrogate for ploidy in human HCC's and corresponding non-tumoral tissues was performed in explant livers from a cohort of 172 patients that underwent liver transplantation.
Results: PIDDosome deficiency increased polyploidy in hepatocytes and reduced DEN-induced tumors in mice. Specifically, tumor multiplicity was significantly decreased in Casp2−/−, Raidd−/− and Pidd1−/− mice as compared to wild type. Irrespective of the genetic background, all tumors contained fewer binucleated cells than the corresponding non-tumoral tissues. CASP2 protein was upregulated in both mouse and human HCCs and correlated with increased Ki-67 levels and with reduced survival, identifying CASP2 as a cell cycle regulated gene. Since liver ploidy in non-tumoral tissue of patients varied with age and with etiology, we defined a tumor ploidy index adjusted for non-tumoral tissue of each patient. Patients with lower ploidy in the tumor as compared to non-tumoral tissue presented with shorter overall (OS) and recurrence-free survival.
Conclusion: The PIDDosome regulates hepatic ploidy and thereby impacts on hepatocarcinogenesis by promoting HCC tumor development from low-ploidy cells as well as on HCC progression and patient OS. Morphometric assessment of the ploidy index may represent a prognostic tool to predict survival in patients with HCC.

FRI504
TERT promoter mutations and liver carcinogenesis: identification and quantification of mutation status by digital PCR analysis on formol-fixed paraffin-embedded samples
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Background and Aims: Liver carcinogenesis follows a sequential process with the development of dysplastic nodules (DN) associated with accumulation of genetic abnormalities, which may progress to hepatocellular carcinoma (HCC). The hotspot mutations of the Telomerase Reverse Transcriptase promoter (pTERT) (main mechanism of telomerase reactivation) are the most observed genomic alterations (20% and 60% of dysplastic nodules and HCC, respectively). As differential diagnosis between DN and HCC is challenging, especially on biopsy specimen, we aimed to detect the pTERT hotspot mutations from paraffin sections of macronodules <2 cm developed on cirrhosis in order to identify those already engaged in the process of malignancy, whatever their morphological classification.
Method: 167 macronodules developed on cirrhotic liver in 33 patients were retrieved, reviewed and morphologically classified as HCC, high grade DN, low grade DN and regenerative nodule. The hotspot (−124), (−146) and (−57) mutations were searched by digital droplet PCR (ddPCR) from macrodissected formalin-fixed macronodules.
Results: Among the 167 macronodules, pathological diagnosis was HCC (64, 38%), high grade DN (18, 11%), low grade DN (15, 9%), and regenerative nodules (27, 16%). In 10 nodules (6%), the diagnosis was difficult (HCC vs high grade DN). For each patient, a cirrhotic nodule (nodule control) was selected for molecular analysis. A total of 52 nodules had a pTERT mutation including 48 in position (−124), 2 in position (−146) and 2 in position (−57). Sixty percent of patients (n = 21) had at least one mutated nodule. Mutated nodules morphologically corresponded to HCC (45.72%), high grade DN

(3.16%), low grade DN (1.7%), regenerative nodule (1.4%) and cirrhotic nodule (1.3%). Of the 10 nodules difficult to classify, one (high grade vs HCC) was mutated (−124). In the set of mutated nodules, the mean allelic frequency of the mutation (−124) was 28.7%, 23.5% for the mutation (−146) and 16% for the mutation (−57).
Conclusion: This study demonstrates the feasibility of ddPCR for searching pTERT mutations from fixed macronodules (including biopsy), and reports for the first time mutation in position (−57). This approach may help to better discriminate the macronodules <2 cm already engaged in the process of malignancy, regardless of their morphological classification.

FRI505

The role of insulin degrading enzyme in gender disparity of hepatocellular carcinoma progression and sorafenib response

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Background and Aims: Hepatocellular carcinoma (HCC) occurs more frequently and aggressively in men than women. However, the underlying mechanistic of the gender disparity in HCC is obscure. Several candidate genes including insulin degrading enzyme (IDE) were screened. In this study we aimed to identify the role of IDE in gender disparity of hepatocellular carcinoma progression and sorafenib response.

Method: The expression of IDE in sorafenib-resistant HCC cells was analyzed using quantitative real-time PCR and western blot analysis. The prognostic role of IDE was evaluated in data from HCC patients in The Cancer Genome Atlas (TCGA) database and validated in male HCC patients treated with sorafenib. Effects of IDE in sorafenib-resistant HCC cells were analyzed in the half maximal inhibitory concentration (IC50) and proliferation. Association between IDE and androgen receptor (AR) signal pathway was assessed in western blot, immunofluorescence and immunoprecipitation assays. The therapeutic value of agent targeting IDE to combat HCC in combination with sorafenib was investigated in vitro and in vivo.
Results: IDE was found enriched in sorafenib-resistant HCC cells. Male HCC patients with increased IDE were associated with poor prognosis. Knockout of IDE in sorafenib-resistant HCC cells decreased the IC50 for sorafenib. Gene Set Enrichment Analysis suggested IDE was associated with the AR signal pathway, which was confirmed by western blot, immunofluorescence and immunoprecipitation assays. Knockout of IDE in sorafenib-resistant HCC cells suppressed the proliferation and was rescued by overexpression of AR. Bacitracin (BAC), an inhibitor of IDE, synergistically increase the efficacy of sorafenib in vitro and in vivo.
Conclusion: IDE represents a useful biomarker to predict sorafenib sensitivity in male patients with HCC, which provides novel insights into gender disparity. Agent targeting IDE represents a novel sex-specific therapeutic strategy for enhancing the efficacy of sorafenib.

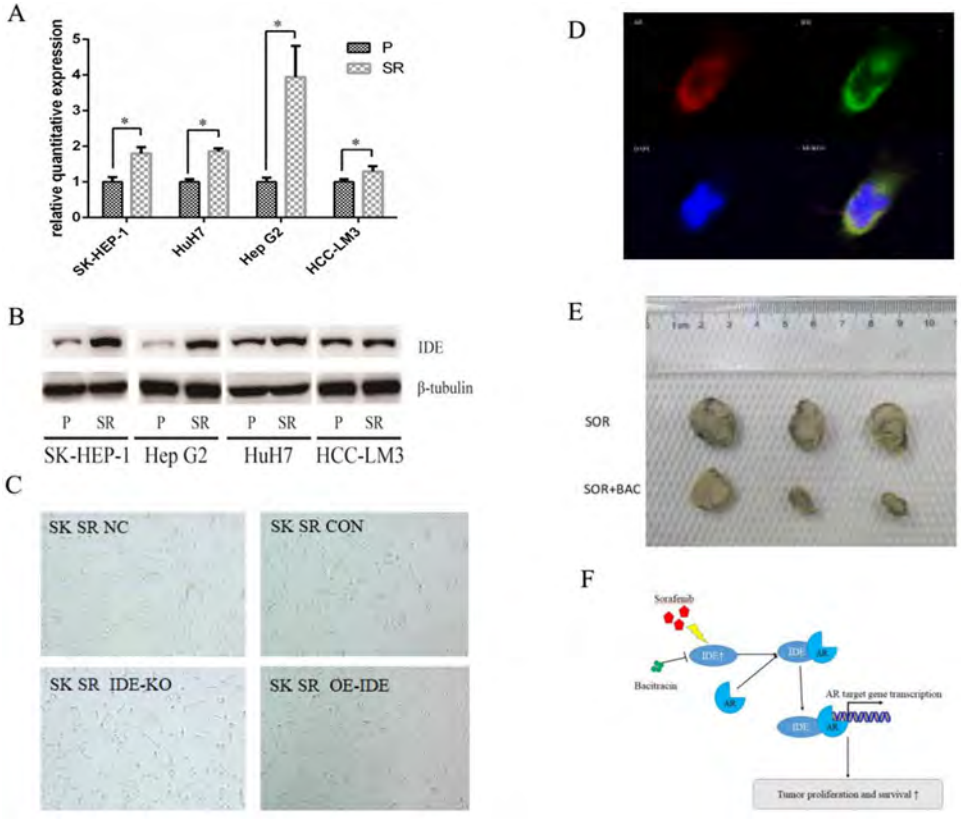

Figure: (abstract: FRI505)

FRI507

A pro-inflammatory variant in the TLR5 gene is associated with hepatocellular carcinoma in patients with cirrhosis due to steatohepatitis.

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Background and Aims: Intestinal bacteria frequently possess flagella, whose structural protein, flagellin, is sensed by the human toll-like receptor 5 (TLR5). Bacterial translocation from the gut is an important mechanism of liver disease progression by stimulating immune response. We wondered whether a variant in a functional TLR5 polymorphism affects development of hepatocellular carcinoma (HCC).
Method: Healthy controls, patients with alcohol abuse but without significant liver disease, and three cohorts of patients with cirrhosis due to alcohol-related or non-alcoholic steatohepatitis with and without HCC were genotyped for the non-synonymous rs5744174 polymorphism in the TLR5 gene. Levels of inflammatory cytokines were measured by ELISA in the serum of patients and in supernatant of stimulated monocytes from healthy controls.
Results: Frequency of the TLR5 rs5744174 TT genotype was similar in healthy controls (n = 212; 33%), controls with alcohol abuse (n = 382; 34%), and patients with alcohol-related cirrhosis in the discovery cohort (n = 372; 28%), the validation cohort (n = 355; 33%) and the cirrhosis cohort of non-alcoholic steatohepatitis (NASH) (n = 139; 28%). However, when patients were stratified according to presence of HCC (n = 79; n = 132; and n = 61 in the respective cohorts), prevalence of the TT genotype was significantly higher in cirrhotic patients with compared to without HCC in the discovery (41% vs 25%), the validation (39% vs 29%) and the NASH cohort (39% vs 22%) (each $p < 0.05$). The association between presence of the TT genotype and HCC remained significant (OR = 1.8; CI 1.1–2.7; $p = 0.01$) after multivariate correction for age (OR = 1.09/year; CI 1.06–1.12; $p < 0.0001$), gender (OR = 3.4; CI 1.9–5.9; $p < 0.0001$), diabetes (OR = 2.2; CI 1.5–3.5; $p < 0.001$), and carriage of the PNPLA3 148M variant (OR = 2.2; CI 1.4–3.5; $p = 0.001$). Interleukin-8 response of flagellin-stimulated monocytes from healthy controls was enhanced in carriers of the TT genotype ($p = 0.02$). Patients with alcohol-related liver cirrhosis carrying the TT genotype had higher serum levels of interleukin-8 (mean 177 vs 61.8 pg/ml; $p = 0.02$) and of CXCL1 (mean 418.1 vs 220 pg/ml; $p = 0.03$).
Conclusion: The TT genotype of the rs57544174 polymorphism in the TLR5 gene is associated with an increased risk for HCC in cirrhosis due to steatohepatitis, which may be linked to enhanced immune response to translocated flagellin.

FRI509

Hepatitis B virus surface antigen inactivates the hippo pathway and thereby increases the hepatic expression of oncogene BMI1

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Background and Aims: Chronic hepatitis B virus (HBV) infection is a key risk factor for the development of hepatocellular carcinoma. Our previous work showed that BMI1 is upregulated in (I) the liver of HBV surface antigen (HBsAg)-transgenic mice, (II) HBV-exposed primary murine hepatocytes (PMH) and (III) HBV-related hepatocellular carcinoma tissue sections. We here investigated the relation between Hippo signalling and BMI1 expression in HBsAg mediated hepatocarcinogenesis.
Method: Reanalysis of GEO (GSE84429) data was performed to search for eligible pathways associated with HBsAg overexpression. PMH were isolated from HBsAg-transgenic or wildtype mice and analyzed by flow cytometry and western blot. Immunocytochemistry staining was performed to intracellularly locate YAP and BMI1 proteins. Dual-luciferase reporter (DLR) assay, chromatin immunoprecipitation (ChIP) was performed to prove the direct regulation of the *Bmi1* promoter by the YAP/TEAD4 transcription factor complex. Short hairpin RNA (shRNA)-induced gene knockdown and overexpression of selected factors were investigated.
Results: Reanalysis of Chip data showed that genes associated with Hippo signalling, cell cycle, centrosomal function and DNA repair/replication were altered in HBsAg-transgenic mice liver. Quantitative PCR and western blot results confirmed that downregulation of MST1/2 is accompanied by loss of YAP phosphorylation and induction of BMI1 expression. Immunohistochemical staining of HBsAg-transgenic mice liver further indicated that expression of HBsAg induced an increase of YAP and BMI1, which resulted in cell proliferation and the abnormal nucleus morphology. Flow cytometry revealed that ploidy and aneuploidy also occurred in PMH of HBsAg-tg mice. Bioinformatic analysis of *Bmi1* promoter indicated the presence of several TEAD4 bind sites. ChIP assay and binding site mutated DLR assays confirmed that YAP/TEAD4 transcription factor complex bound and activated the *Bmi1* promoter. Hepa1-6 cell line was transfected with an RFP-reporter plasmid containing the Bmi1 promoter region, herein knockdown of Yap or Tead4 led to decreased RFP signals.
Conclusion: The Hippo signalling pathway plays a vital role in cell homeostasis. Our findings led to suggest that HBsAg-mediated Hippo pathway inactivation results in BMI1 expression, possibly promoting hepatocarcinogenesis through alteration in cell cycle and chromosomal stability.

FRI510

Natural killer cells target XPO1: a therapeutic opportunity for HCC

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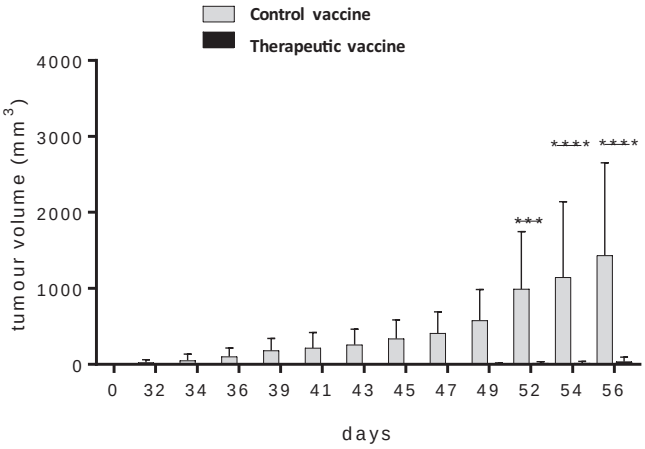
Background and Aims: Despite extensive recent developments in cancer immunotherapy, hepatocellular carcinoma (HCC) remains difficult to treat. Natural killer cells are well known to directly recognise cancerous cells, can regulate the tumour micro-environment and have an emerging therapeutic potential. However, the underlying mechanisms of how NK cells can recognise HCC are still unclear. Our goal was to identify new mechanisms by which NK cells could recognise HCC and explore the therapeutic potential for NK cells in HCC.
Method: MHC class I peptides were eluted from the HUH7 cell line to identify peptides that would bind and activate NK cells. In vitro peptide binding assays and assays of NK cell phenotype and function were performed. Mice were vaccinated with a novel NK cell targeting-DNA vaccine and activation of NK cells assessed using flow cytometry and functional assays. A xenograft model of HCC was used for adoptive transfer experiments of NK cells from vaccinated mice.
Results: From over 6000 peptides sequenced we identified one peptide with the potential to activate NK cells. This peptide, NAPLVHATL, was derived from the nuclear export protein XPO1, which is upregulated in approximately one third of HCCs, and also in other cancers including myeloma, lung, breast and prostate cancer. In vitro, binding of NAPLVHATL to HLA-C was confirmed and it was shown to bind the activating NK cell receptor KIR2DS2 using a tetramer assay. This peptide specifically activated KIR2DS2+ NK cells



NSG mice were inoculated subcutaneously with HUH7 cells and natural killer cells from vaccinated or control vaccinated mice adoptively transferred. Tumour size was monitored (n=4-5 per group)

Figure: (abstract: FRI510)

and siRNA knockdown of XPO1 in HUH7 cells reduced activation of KIR2DS2. Vaccination of KIR-transgenic mice with a KIR2DS2-targeting DNA vaccine increased activation of NK cells in both spleens and livers as determined by KLRG1 expression ($p < 0.01$), and this was most marked on mature CD11b+CD27-KIR2DS2+ NK cells ($p < 0.01$). NK cells from vaccinated mice had peptide–specific NK cell responses in vitro, which were not observed in peptide control vaccinated mice. Adoptive transfer of NK cells from vaccinated mice led to impaired growth of HUH7 cells in NOD/SCID/γ_c KO mice, as compared to NK cells from mice vaccinated with a control vaccine.
Conclusion: We describe the first known HLA class I restricted tumour associated antigen to be targeted specifically by NK cells. We also demonstrate proof-of-concept for an NK cell targeting peptide vaccination strategy for HCC.

FRI511

Myeloid IRE1a deletion alters hepatic macrophage phenotype and attenuates experimental non-alcoholic steatohepatitis-related hepatocellular carcinoma

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Background and Aims: Obesity, diabetes and associated non-alcoholic steatohepatitis (NASH) are characterized by adipose tissue and hepatic fat accumulation and inflammation and are rising causes of hepatocellular carcinoma (HCC). Macrophages are important immune cells involved in inflammation and tumour development. Inositol-requiring enzyme 1 alpha (IRE1a) has shown to be involved in macrophage cytokine production and myeloid-specific IRE1a knock-out (mKO) mice showed reduced weight gain during high fat diet feeding. However, the effect of myeloid-specific IRE1a deletion on NASH and subsequent HCC development has not been examined.
Method: Mice with non-functional myeloid IRE1a were created by crossing IRE1a floxed mice with LysM-Cre mice. Two-day old mKO and wild type (WT) mice were subcutaneously injected with streptozotocin (STZ) or PBS as control and male mice were fed a high-fat, -sucrose, -cholesterol diet (Western diet, WD) or control diet from the age of 4 weeks until 21 weeks. Mice were evaluated for obesity, diabetes, NASH and HCC. The macrophage population was evaluated by flow cytometry and RNA sequencing on FACS isolated cells.
Results: STZ+WD feeding resulted in impaired glucose tolerance, advanced NASH with fibrosis and HCC development. mKO STZ mice showed lower fasting glucose levels at the start of WD feeding, and an improved glucose tolerance and attenuated HCC development after 17 weeks of WD feeding despite a similar degree of liver steatosis and inflammation compared to WT mice. Transcriptomic analysis of liver Kupffer cells (KCs), macrophages and monocytes revealed phenotypical changes in NASH-HCC. Myeloid IRE1a deletion in healthy mice resulted in an altered transcriptomic profile with downregulation of pathways involved in immune system activation in KCs and macrophages, downregulation of metabolic pathways in KCs, whereas pathways involved in cell division and metabolism were upregulated in monocytes. Macrophages showed both up- and downregulated metabolic pathways. NASH-HCC attenuated the differential gene expression profile of mKO and WT liver isolated macrophages.
Conclusion: Our results show that myeloid-specific IRE1a deletion results in an altered transcriptional profile of hepatic macrophages and attenuates diabetes induction and NASH-related HCC development.

FRI512

TAK1 is a novel therapeutic target for hepatocellular carcinoma and contributes to sorafenib resistance

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Background and Aims: TAK1 has a dual role in cancer development and is associated with drug resistance in HCC. The upregulation and activation of TAK1 in intermediate and advanced HCC remains unclear. Mechanistically, little is known about K48-linked ubiquitination and proteasomal degradation of TAK1. This article aims to uncover the mechanism of TAK1 overexpression and its contribution to sorafenib resistance in HCC, and to verify whether targeting TAK1 pharmacologically could be a promising combinational therapy with sorafenib.

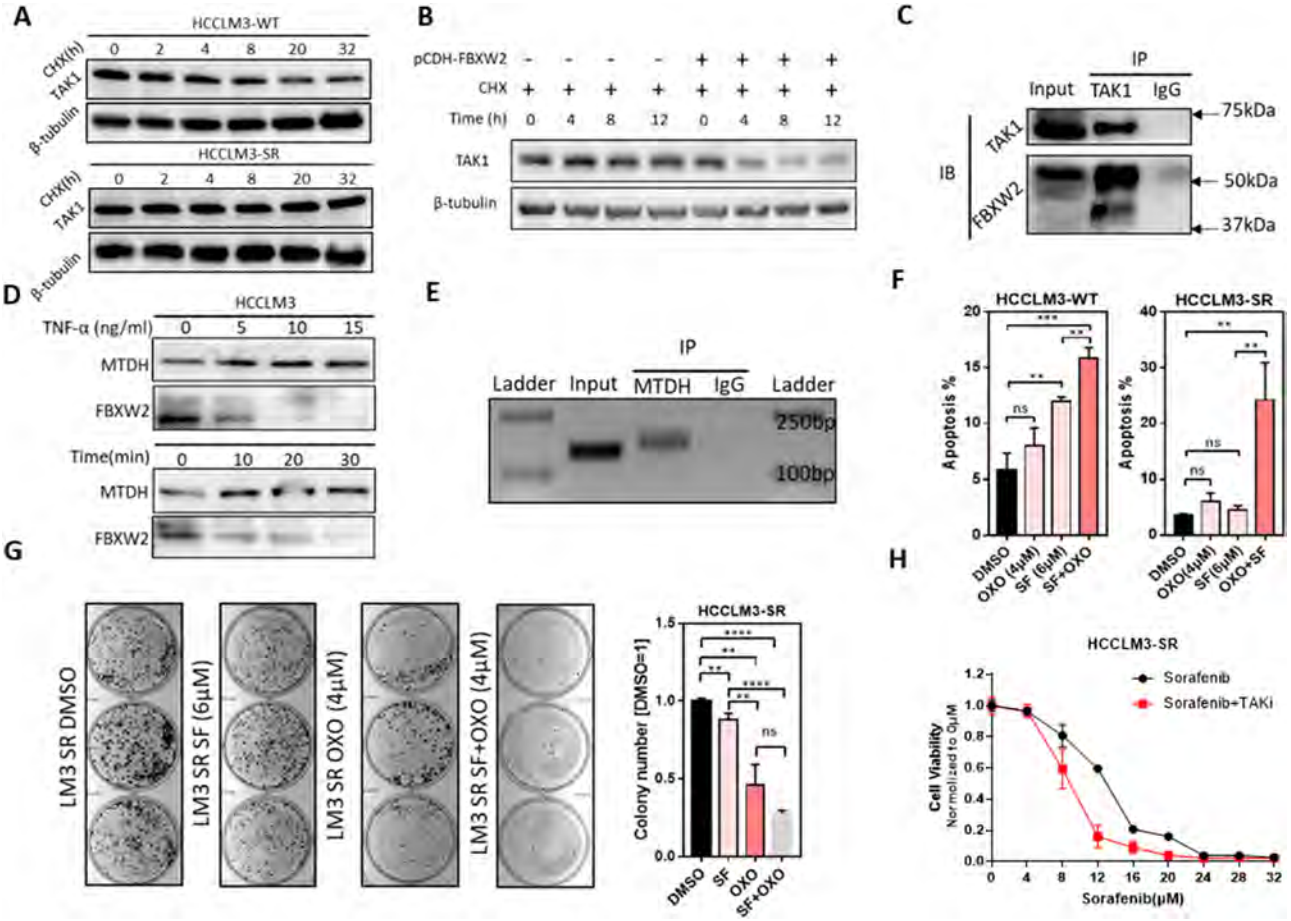

Figure: (abstract: FRI512)

Method: The expression level of TAK1 has been estimated in HCC cell lines and HCC patients by western blot. The prognostic prediction value of TAK1 has also been estimated in HCC patients receiving sorafenib treatment. CHX assay and Co-Immunoprecipitation has been conducted to measure the half-life of TAK1 protein and to determine the physical binding of TAK1 and its E3 ligase. Multiple in vitro and in vivo assays have been conducted to determine the synergistic effects and the involved mechanism between the combination of TAK1 inhibition and sorafenib.
Results: We found that TAK1 was overexpressed in HCC cell lines and HCC patients. High expression of TAK1 in patients receiving sorafenib was associated with unfavorable outcomes. Sorafenib induced apoptosis via inhibiting the phosphorylation of TAK1 in HCC cell lines, while suppressed ubiquitin-mediated degradation of TAK1 potentiated the development of sorafenib resistance. We identified FBXW2 downregulated in sorafenib-resistant cells as a novel E3 ligase binding to TAK1 via specific motif TSXXXS. Moreover, MTDH that has been widely involved in chemotherapy resistance negatively regulated the stability of FBXW2 mRNA. In turn, TAK1/CEBPB increased the expression of MTDH, forming a positive feedback loop in promoting NF-κB pathway. At last, treatment with 5Z-7-Oxozeaenol, a TAK1 inhibitor, significantly induced apoptosis of HCC cell lines and restored sorafenib sensitivity in sorafenib-resistant cells. Sorafenib and Takinib, a specific TAK1 inhibitor, had synergetic effect killing HCC cells.
Conclusion: Our data uncovered the underlying mechanism of suppressed degradation of TAK1 in HCC and sorafenib resistance. The striking synergetic effect of TAK1 inhibitors and sorafenib may promote innovative combination therapies for HCC.

FRI513

Exposing the regulation of MDM2 expression by ADAR-mediated A-to-I editing in human hepatocellular carcinoma: application of a large-scale on-step predicting platform in oncology research

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Background and Aims: Adenosine-to-inosine (A-to-I) editing induced by ADAR family proteins is one of the most common endogenous modifications during post- and co-transcription. This modification on double-stranded RNA may disturb normal mRNA translation, alternative splicing and miRNA-3′UTR binding, and further affect multiple cellular process and functions. Previously, several studies have demonstrated that a disrupted A-to-I editing balance has biological implication in hepatocellular carcinoma (HCC) development. However, the regulatory mechanism of A-to-I editing in HCC still needs to be elucidated via accurate large-scale bioinformatics analysis.
Method: RNA high-seq data from 35 pairs of human HCC patients were analysed to identify the A-to-I editing events using REP, our predicting platform which can automatically distinguish all A-to-I editing events by their potential downstream effects, and eliminate the editing sites without downstream function. The downstream effects of these functional editing sites on each gene were further analysed.

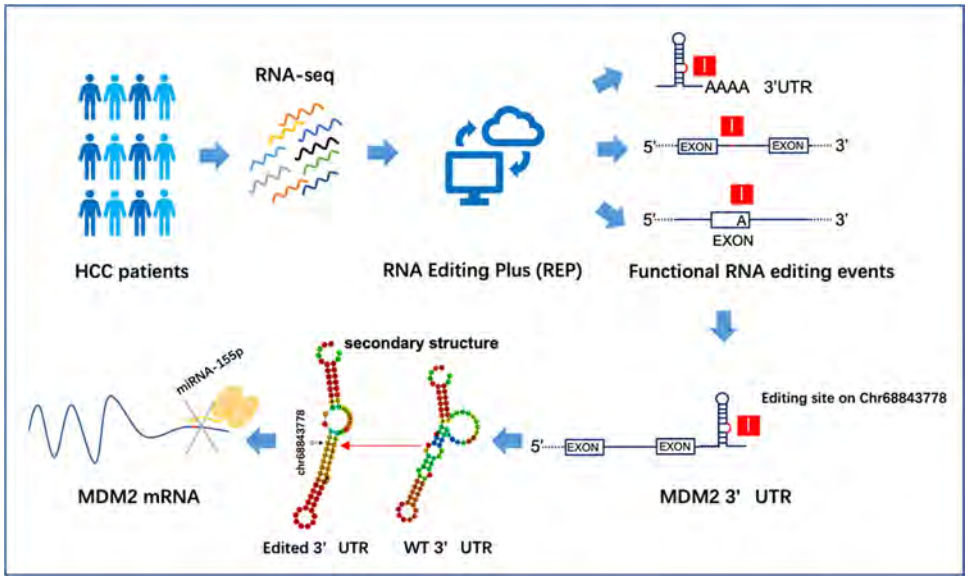

Figure: (abstract: FRI513)

Results: The results showed that the expression level of ADAR1 and the A-to-I editing level in HCC tissues significantly higher than para-carcinoma tissues. Top 5 genes (METTL7A, VHL, MDM2, APOL6, XIAP) with the highest level of A-to-I editing were identified. After removing the editing events without downstream effects, we obtained 5 genes (METTL7A, MDM2, APOL6, XIAP, PAICS) with the highest level of functional editing. Most of these 5 genes are reported oncogene or tumor suppressor. Previously, Qi et al. has reported the downregulation of METTL7A by ADARs promote HCC development. Here, we performed an in-depth analysis of all of functional editing sites that occurred on MDM2, the second frequently edited gene in HCC. Importantly, our results showed that the expression of MDM2 in HCC cells is positively correlated with the level of A-to-I editing at site chr68843778 which located in 3′UTR region of MDM2. This novel editing on chr68843778 leads to the secondary structure change in 3′ UTR region, resulting in alteration of miRNA-155p-MDM2 targeting efficiency. Besides, non-classical regulatory manner was also detected. The increased expression of MDM2 enhances the proliferation and migration of HCC cells.
Conclusion: Our data confirm that A-to-I editing is closely related to the development of HCC, and will provide a basis for the research of the regulatory mechanism of A-to-I RNA editing in HCC.

FRI514
Androgen receptor sensitized sorafenib efficacy via enriched EPCAM stemness in hepatocellular carcinoma

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Background and Aims: Androgen Receptor (AR) bimodal function has been discussed in Hepatocellular carcinoma (HCC) that promote initiation and suppress progression. However, the translational value of AR roles in HCC is unknown. Sorafenib, the multiple kinase inhibitor, is considered as the standard adjuvant therapy for unresectable HCC patients. This study aimed to evaluate the impact of AR in Sorafenib intervention in HCC laboratory models.
Method: AR cDNA was introduced in HCC cells to test AR function, cancer characteristics, and Sorafenib cytotoxic I.C.50. Knockout hepatic AR in carcinogen and HBV-induced HCC mouse models to examine AR effect on marker gene expressions. Quantitative PCR and immunoblot for testing AR effect on gene expressions. Cell sorting with stemness surface antigens to examine Sorafenib effect in vitro and in vivo. At last, bioinformatics for associating AR or EPCAM expressions with prognosis.
Results: Using in vitro model, AR cDNA stable expressing cells exhibited excellent transactivation function, better colony and sphere forming activities, and facilitated tumorigenicity capacity compared to parental HCC cells. While examining stemness markers, EpCAM was dramatically increased upon AR expression. Consistently, EpCAM+ cells was significantly decreased in spontaneous HCC AR knockout HCCs, compared to that of wildtype littermates. AR also ablated Sorafenib downstream signals, e.g., ERK, AKT, and p38MAPK, while they were been upregulated in parental cells. As for Sorafenib cytotoxic effect, the AR expressing cells are vulnerable to treatments. Moreover, sorting EPCAM or CD133 from HCC sphere cells, the IC.50 of Sorafenib were drastically lowered in AR+/EPCAM+ compared to AR–/EPCAM–. Strikingly, Sorafenib IC.50 are similar between AR+/CD133+ vs. AR–/CD133+ cells. Besides, Sorafenib regimen was robust suppress tumor growth in AR+/EPCAM+, but not AR–/EPCAM– implanted cells. At last, bioinformatics analysis revealed EPCAM is prognostic biomarkers in Asian and non-alcohol consumption HCC patients, suggesting a targeting value in those patients.
Conclusion: AR+/EPCAM+ could be therapeutic responsiveness marker for HCC patients receiving Sorafenib, particularly in Asian and non-alcohol related HCC. It's important to conduct an prospective survey associating AR/EPCAM expression to therapy outcomes.

FRI515

BAP1 loss in hepatocellular carcinoma is associated to PKA activation and fibrolamellar features

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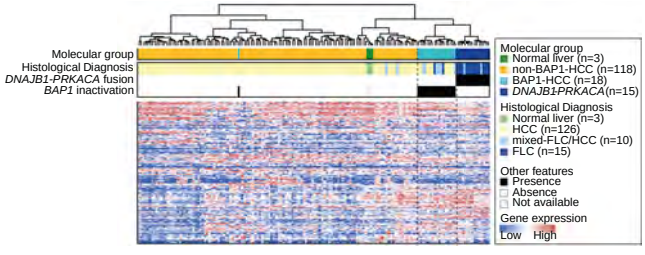
Background and Aims: Fibrolamellar carcinoma (FLC) is a rare subtype of hepatocellular carcinoma (HCC). In adolescents and young adults, all FLC are driven by a specific *DNAJB1-PRKACA* fusion inducing an over-activation of the cAMP-dependent protein kinase (PKA) pathway. However, tumors harbouring mixed histological features of HCC and FLC (mixed-FLC/HCC) also occur in older patients and their genomic landscape remains to be explored.
Method: In this French multi-centric study, histological reviewing was performed in 151 selected liver tumors including 126 HCC, 15 FLC, and 10 mixed-FLC/HCC. RNAseq and whole-genome- or whole-exome-sequencing was performed on all 151 tumors, and 340 non-selected tumors from the TCGA cohort were used for validation. Genomic discoveries were validated with western-blot and immunohistochemistry.
Results: Hierarchical clustering on the transcriptomic data identified a subgroup of 17 tumors all harboring a biallelic inactivation of the *BAP1* tumor suppressor (BAP1-HCC) and regrouping most of the mixed-FLC/HCC (Figure). Compared to non-BAP1-HCC, BAP1-HCC shared a lot of features with FLC, at the clinical level (enrichment in females, lack of chronic liver disease), at the histological level (high intratumor fibrosis) and at the molecular level (significant exclusion with the classical HCC drivers such as *CTNNB1*, *TP53* and *TERT* promoter, expression of markers of hepato-pancreatic progenitors). However BAP1-HCC patients were older and had a poorer prognosis than FLC patients. BAP1-HCC were devoid of the *DNAJB1-PRKACA* fusion but instead showed recurrent gains / amplifications of the *PRKACA* locus, together with a loss of the *PRKAR2A* locus (coding for the inhibitory subunit of PKA), leading to a high PRKACA/PRKAR2A ratio at the mRNA and protein levels.



Conclusion: *BAP1* loss, found in around 5% of HCC, defines a homogeneous group of tumors with fibrolamellar-like features and an alternative dysregulation of the PKA pathway through copy-number alterations. This common over-activation of PKA could explain the similarities between BAP1-HCC and *DNAJB1-PRKACA* FLCs, and could extend the number of liver tumors susceptible to future PKA-targeted therapies.

FRI516

PPEF2 suppresses hepatocellular carcinoma by inhibiting c-Myc signal pathway

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Background and Aims: Primary liver cancer ranks the sixth most commonly diagnosed cancer worldwide, of which hepatocellular carcinoma (HCC) is the major type. The outcome of HCC is very poor, and the development mechanism still is not fully understood. In a previous study, we performed a genome-wide loss of heterozygosity (LOH) analysis on 104 HCCs with microsatellite genotyping and found that D4S2964 locus has a 50% LOH. Then we conducted another LOH analysis on 112 HCC samples with a custom single nucleotide polymorphism (SNP) genotyping microarray and identified PPEF2 gene with 64.5% LOH in D4S2964 locus. In this study, we aimed to explore the clinical significance, biological function and mechanism of PPEF2 in HCC.
Method: Taqman PCR was conducted to detect the DNA copy number of PPEF2. Quantitative real-time reverse transcription-PCR (qRT-PCR) was performed to measure PPEF2 mRNA expression level in fresh HCC and non-cancer liver samples. Immunohistochemistry (IHC) staining was used to examine PPEF2 protein expression in three cohorts of HCC cases and the relationship between PPEF2 and clinical characteristics was analyzed. The biological functions of PPEF2 in hepatocarcinoma cells were explored in vitro and in vivo. The co-immunoprecipitation assay was conducted to ensure the interaction between PPEF2 and c-Myc. The alteration of c-Myc and downstream target was examined by western blot.
Results: The LOH of PPEF2 was detected in 86.1% (68/78) of HCC patients and the mRNA expression of PPEF2 was significantly down-regulated in HCC tissues, which is associated with poor prognosis in HCC patients. PPEF2 protein level also is notably reduced in HCCs compared with matched liver tissues as showed by western blot and IHC detection. Importantly, PPEF2 protein expression measured by IHC is significantly correlated with overall survival and disease-free survival in 3 cohorts of HCC patients. PPEF2 suppressed the proliferation of hepatocarcinoma cells in vitro, and inhibited the colony formation and induced the G1/S arrest of HCC cells. Mechanistically, PPEF2 protein, which mainly located in cytoplasm, is interacted with c-Myc and reduces its protein level by accelerating the ubiquitinated degradation of c-Myc protein, which caused negative regulation of cyclins and cyclin dependent kinases (CDKs).
Conclusion: PPEF2 expression is a potential prognostic biomarker in HCC patients and suppresses HCC cell proliferation by down-regulating c-Myc protein level.

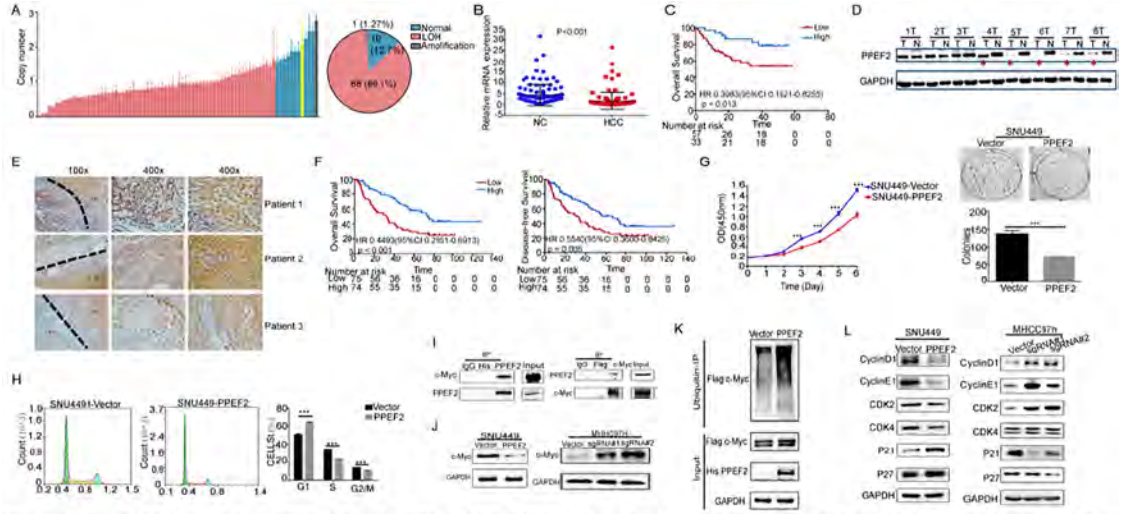

Figure: (abstract: FRI516)

FR518

Hepatic activation of FOXO3 triggers positive feedback-loop for mTORC2-Akt and enhances oxidative damage-associated hepatocellular carcinogenesis

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Background and aims: Hepatocellular carcinoma (HCC) is the most prevalent primary liver cancer, accounting for 80–90% of cases. Mutations are commonly found in the signaling regulating the Akt pathway, leading to oncogenic cell proliferation and survival. Key transcription factors that are negatively regulated downstream of PI3K/Akt are members of the forkhead box O family (FOXO). FOXOs were initially considered as tumor suppressors by inducing cell cycle arrest and apoptosis. However, there is increasing evidence showing that FOXOs, especially FOXO3, can support tumorigenesis.

Method: To understand the roles of FOXO3 in liver tumorigenesis and hepatocarcinogenesis, we analyzed HCC patient specimens and also established a doxycycline-regulated transgenic mouse model with hepatocyte-specific FOXO3 expression in a constitutively active form.

Results: We found that FOXO3 protein is significantly overexpressed and activated in livers of HCC patients. Hepatic activation of FOXO3 induced extensive hepatic damage and elevated gene expression of several HCC-associated factors. Furthermore, FOXO3 expression enhanced hepatotoxicin-induced tumorigenesis. Mechanistically, FOXO3 activation caused oxidative stress and DNA damage and triggered positive feedback-loop for Akt activation as well as mTORC2 activation. Interestingly, FOXO3 activated not only reactive oxygen species (ROS)-promoting pathways, but also ROS-eliminating systems, which can be associated with the activation of the pentose phosphate pathway.

Conclusion: FOXO3 is a master regulator of ROS. On one side, FOXO3 supports in protecting from ROS and may avoid cellular crisis but FOXO3 can also promote ROS signaling on the other side and support hepatocellular carcinogenesis.

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NAFLD: Experimental and pathophysiology

SAT001

Lipoprotein lipase deletion induces a proinflammatory phenoytpe in liver-infiltrating monocytes during non-alcoholic steatohepatits

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Background and Aims: While absent in the healthy liver, hepatic expression of lipoprotein lipase (LPL) is upregulated during non-alcoholic steatohepatitis (NASH). The functional consequence is unclear, however. We have previously shown that LPL deficiency in myeloid cells leads to a more severe NASH phenotype. Published evidence suggests that LPL may influence macrophage polarization. The aim of our current study was to evaluate if LPL deficiency affects myeloid cells during NASH progression.
Method: C57BL/6J mice heterozygous for lysozyme2-cre recombinase were crossed with LPL floxed mice to generate mice with a myeloid cell-specific LPL knockout ($LPL^{\Delta LysM}$) and wild type-like littermates ($LPL^{fl/fl}$). Mice were fed a high cholesterol, high fat, high caloric diet for 26 weeks to induce a NASH. The NASH phenotype was characterized by histology, qPCR and transaminases. Liver cells were isolated and analyzed by flow cytometry.
Results: We could reproduce our previous finding that myeloid cell-specific LPL knockout aggravates the NASH phenotype with enhanced fibrosis and inflammation in $LPL^{\Delta LysM}$ mice. Immune cell phenotyping showed increased number of CD8+ T cells in the livers of $LPL^{\Delta LysM}$ NASH mice compared to $LPL^{fl/fl}$ NASH mice. LPL deficiency in myeloid cells did not influence the frequency of different myeloid cell populations in liver or blood. The percentage of neutrophils (Ly6Ghigh), monocytes (Ly6Gnegative, Ly6Chigh) and liver resident macrophages (F4/80high) remained on a comparable level in both NASH groups. Liver monocytes produced more iNOS indicating a stronger proinflammatory phenotype in liver infiltrating LPL-deficient monocytes in NASH. In contrast, the immunophenotyping of liver resident macrophages and peripheral monocytes did not show any differences between $LPL^{fl/fl}$ and $LPL^{\Delta LysM}$ NASH mice.
Conclusion: LPL deficiency in myeloid cells aggravates NASH progression. In NASH, LPL appears to restrict a proinflammatory phenotype in liver-infiltrating monocytes but not in liver resident macrophages.

SAT002

A translational mouse model for NASH and advanced fibrosis in association with atherosclerosis

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Background and Aims: Non-alcoholic steatohepatitis (NASH) is a fast-growing liver disorder in the Western world and is associated with an increased incidence of cardiovascular disease and type 2 diabetes. Animal models adequately mimicking this condition and that display both the metabolic and histological features of human NASH are scarce. We herein investigate whether Ldlr−/−.Leiden mice on a high fat diet represent a suitable NASH model.
Method: Ldlr−/−.Leiden mice were fed high-fat diets (no added cholesterol) containing lard or milk fat for 28 weeks. Effects on body weight, plasma and liver biochemical variables, liver histology, adipose tissue (inflammation) and atherosclerosis (aortic root) were assessed. Additionally, disease induction at earlier timepoints in the milk-fat group were investigated by taking a liver biopsy at t = 12 weeks and sacrifice at t = 22 weeks. The response to treatment (week 18–28) with 10 mg/kg/d FXR agonist obeticholic acid (OCA) on NASH and fibrosis was also evaluated.
Results: Both high-fat diets induced obesity, hyperlipidemia, hyperinsulinemia, and increased ALT and AST levels. Mice on both diets developed progressive macro- and micro-vesicular steatosis, hepatic inflammation and fibrosis. OCA treatment significantly reduced hepatic inflammation and fibrosis in both models. Lard-fat diet group had more severe hyperinsulinemia and adipose tissue inflammation, while milk-fat diet group had more severe hepatic inflammation with advanced bridging fibrosis (F3) in all mice after 28 weeks. Another longitudinal study with the milk fat diet revealed that after 22 weeks on the diet fibrosis was significantly induced, but primarily in F1-F2 stage with occasionally bridging fibrosis. In addition, milk-fat diet induced severe atherosclerotic lesions (primarily type IV and V based on AHA classification) in the aortic root area after 22 weeks.
Conclusion: Ldlr−/−.Leiden mice fed high-fat diets recapitulate features of the metabolic syndrome and NASH with progressive liver fibrosis and simultaneous atherosclerosis development. By adaptation of the fat content of the diet, either insulin resistance and adipose tissue inflammation (lard-based diet) or hepatic inflammation and fibrosis (milk-fat diet) can be emphasized. This represents a novel translational animal model of fibrosing NASH in association with atherosclerosis that can be used to investigate the effects of new drugs, alone (or drugs in combination).

SAT003

Aberrant hepatic protein tyrosine phosphatase receptor type delta expression is a driver of metabolic liver disease

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ELSEVIER

Background and Aims: Chronic hepatitis C virus (HCV) infection is a major cause of hepatic steatosis and metabolic disease. We previously demonstrated that HCV infection impairs protein tyrosine phosphatase receptor type delta (PTPRD), a candidate tumour suppressor associated with poor prognosis and enhanced signal transducer and activator of transcriptions (STAT3) transcription (Van Renne, Roca Suarez et al. Gut 2018). Since HCV-induced STAT3 activity perturbs peroxisomal beta-oxidation (Lupberger et al. Gastroenterology 2019) and somatic mutations of PTPRD associate with diabetes type II (Chen et al., Oncotarget 2015), we aim to study the role of PTPRD as regulator of hepatocyte metabolism and liver disease.
Method: Based on liver transcriptomic data, non-infected normal and obese patients were classified according to hepatic PTPRD expression levels and diabetic blood markers. Gene set enrichment analysis (GSEA) was performed in order to identify signalling pathways associated with low PTPRD expression. Results were validated in primary human hepatocytes (PHH) by RNAi and western blotting, and in livers of PTPRD-deficient mice following 8 weeks of choline-deficient high-fat diet (CD-HFD) feeding.
Results: Livers of normal patients with low PTPRD expression exhibit an enrichment of genes associated with peroxisomal function, inflammation and glucose metabolism suggesting PTPRD as regulator of hepatic fat metabolism and insulin signalling. Indeed, silencing PTPRD in PHH impairs Akt phosphorylation following insulin stimulation. Livers of PTPRD-deficient mice (Ptprd+/–) mice exhibit higher STAT3 phosphorylation levels and present hepatic transcriptional changes similar to healthy patients with low PTPRD levels. Moreover, induction of liver disease in PTPRD-deficient mice using CD-HFD cause a diabetic phenotype including increased fasting blood glucose levels in absence of weight gain in Ptprd+/– animals. In obese patients with low hepatic PTPRD expression, we found increased blood levels of fasting glucose, glycated haemoglobin (HbA1c) and elevated insulin resistance scores (HOMA2).
Conclusion: Our data suggests an important regulatory role of the hepatic PTPRD-STAT3 axis in fatty acid and glucose homeostasis, which is associated with clinical manifestations of metabolic disease. We suggest that targeting PTPRD downstream signalling represents a potential strategy to restore metabolic pathways and hepatic steatosis in risk patients.

SAT004
LncRNA-H19 as a marker of liver progression from steatosis to hepatocellular carcinoma

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Background and Aims: The main aims of this study were: a) Isolation, characterization and analysis of the epigenetic profile of liver cancer stem cells (LCSC) b) Assessment of *H19* in a NAFLD-HCC animal model c) Validation of *H19* as a diagnostic biomarker in HCC patients.
Method: a) *In vitro* LCSC were isolated from a Huh7.5 cell line by FACS ($EpCAM^+CD133^+$) and *H19* expression was evaluated by qPCR b) A total of 31 6w-old male C57BL/6J were fed with a HFHCC diet (40% Kcal-fat, 1%cholesterol and 42 g/L glucose/fructose in drinking water) (n = 26) or standard diet(n = 5) for 52w. Histological, biochemical and metabolic profiles were measured and *H19* liver expression was assessed by qPCR c) *H19* levels were determined in 14 liver tissues from cirrhotic patients, with HCC (n = 7) or without (n = 7). Circulating *H19* was evaluated in 67 patients; 26 with liver cirrhosis without HCC at baseline (of them, 6 developed HCC during follow-up) and 41 suffering from HCC. Total RNA was isolated from plasma and the quantification of *H19* copies was performed by using digital droplet PCR (ddPCR).
Results: a) An increase in size and number of spheroids was observed in $EpCAM^+CD133^+$ cells (LCSC *vs.* Huh7.5: fold-sphere number: 2.15 ± 0.96; p = 0.004 and fold-size μm^2: 3.04 ± 1.93; p < 0.001). LCSC showed higher expression of *H19* levels than Huh7.5 (fold-2.18 ± 0.32; p = 0.003) b) HFHCC-diet induced steatosis within the first 39w and NASH at 52w. Nodules were detected in 33% of mice, being classified into adenomas or well-differentiated HCC. *Gpc3*+ expression was significantly raised in presence of HCC (p < 0.0001). *H19* was upregulated in NASH and HCC liver tissue when compared to steatosis (p = 0.05 and p = 0.001) and control group (p = 0.011 and p = 0.016). Also, *H19* was increased in ballooning (p = 0.003), oval cells proliferation (p < 0.001) and advanced fibrosis (p = 0.010). There was not found association with steatosis and lobular inflammation c) *H19* was found significantly increased in liver tissue from HCC patients compared to cirrhotic patients (fold-4.0 ± 2.55; p = 0.020). In addition, *H19* was found upregulated in plasma from HCC *vs.* cirrhotic patients without development of HCC (2.60 ± 2.29 *vs* 1.02 ± 0.58 copies/µL; p < 0.001). Cirrhotic patients who developed HCC during the follow-up period showed higher levels of *H19* compared to non-HCC cirrhotic patients (4.42 ± 3.96 *vs* 1.02 ± 0.58, copies/ul p = 0.089).
Conclusion: H19 was found to be increased in LCSC, promoters of the carcinogenesis. Also, it was found upregulated in both NASH and tumors in a NAFLD preclinical model, as well as in liver tissue and plasma from HCC patients. Therefore, H19 could constitute a biomarker of disease progression from liver steatosis to HCC.

SAT005
The lipid composition of the liver: assessing differences in obese patients with and without non-alcoholic steatohepatitis

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Background and Aims: Obesity and associated co-morbidities are reaching pandemic proportions in developed countries. Non-alcoholic steatohepatitis (NASH) is the hepatic co-morbidity of this disease and is gaining interest due to the metabolic importance of the liver. The aim of our study was to assess the lipid composition of the liver from patients with obesity and with or without NASH.
Method: Obese patients were divided into NASH group (n = 50) or non-NASH group (n = 50) depending on their non-alcoholic steatohepatitis activity score (NAS). To assess the liver lipid composition, 10 mg of liver were homogenized and lipids were extracted by using a solution of chloroform – methanol (2: 1 proportion). After different centrifugation, the apolar phase was dried, reconstituted in methanol – MTBE (9: 1 proportion) and placed into vials for the UHPLC-ESI-QTOF-MS.
Results: Cholesterol esters were the main lipid species in the liver composition. The lipid categories present in the livers were similar in patients with and without NASH. However, their concentrations and therefore percentages were different: especially note cholesterol esters, which were statistically increased in obese patients with NASH (70.9% in non-NASH vs 89.8% in NASH) (Figure 1A). We observed that all lipids were generally increased in livers with NASH, except phospatidylcholines, which were all decreased (Figure 1B). In a

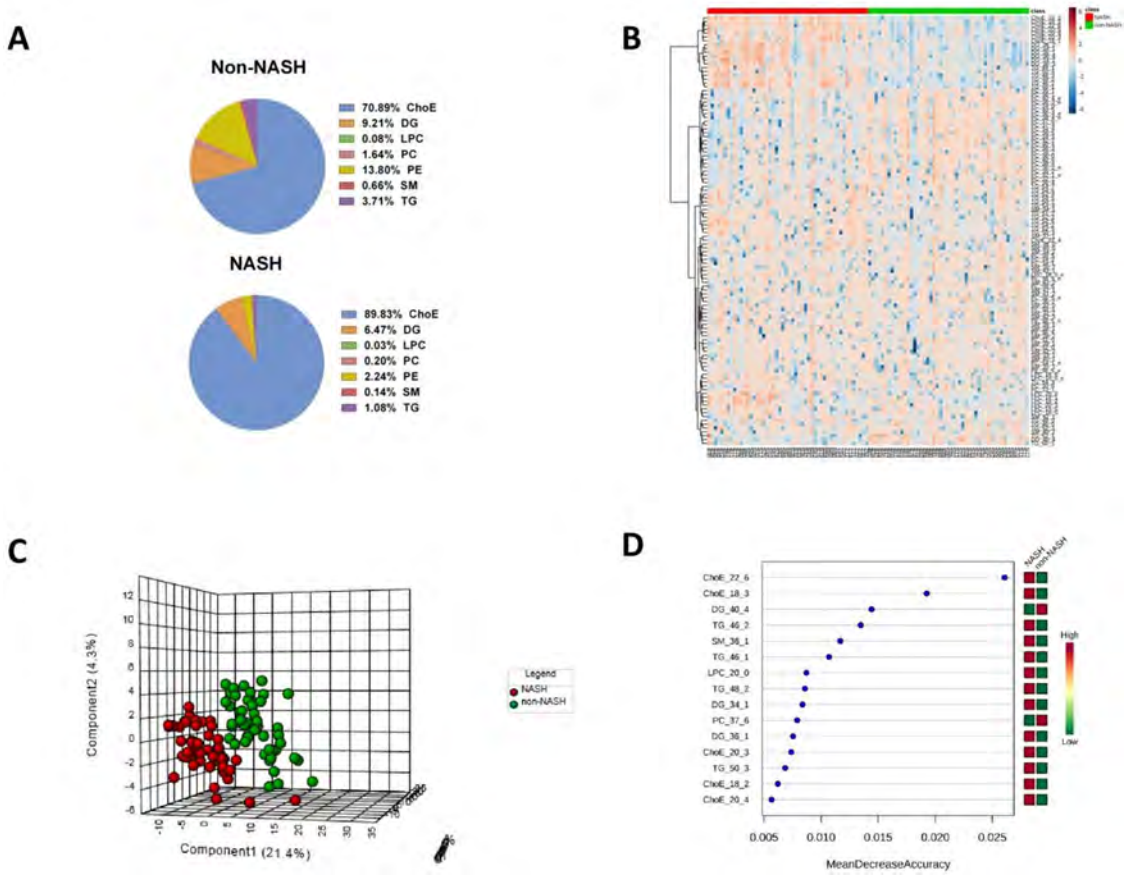

Figure: (abstract: SAT005)

PLSDA, the combination of liver lipid compounds allowed a correct separation of patients with and without NASH (Figure 1C). Finally, by using a random forest analysis, we saw that two cholesterol esters were the lipid species with the best discriminant capacity between NASH and non-NASH patients: Cholesterol esters 22:6 and 18:3.
Conclusion: The lipid composition of the liver is different when obese individuals suffer from NASH. These changes in lipid concentration could point to new possible molecular mechanisms of this disease which may be related to lipid dysregulation.

SAT006

AXL inhibition prevents NAFLD progression in mice with soluble AXL as marker of the NAFLD to NASH transition

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Background and Aims: TYRO3, AXL and MERTK are receptor tyrosine kinases activated by the ligand GAS6. AXL signalling is increased in NASH patients, promotes fibrosis in hepatic stellate cells and inflammation in Kupffer cells, while GAS6 protects hepatocytes against lipotoxicity via MERTK. Recent data has shown that the AXL kinase inhibitor bemcentinib, by blocking AXL signalling and increasing GAS6 levels, reduces experimental NASH. However, AXL's role in the NAFLD/NASH transition has not been addressed. Identifying mechanisms responsible for NAFLD progression into NASH could provide early markers and novel therapeutic targets.
Method: Mice were fed a high-fat methionine-restricted choline-deficient (HFCD) diet for 2 and 4 weeks, and a high-fat diet with fructose (HFF) for 4 months to induce different degrees of NAFLD/NASH. Mouse Gas6, soluble levels of Axl (sAXL) and Mertk were measured by ELISA. Human GAS6, sAXL and MERTK were measured by ELISA in control and patient serum, and compared with biochemical and histological data. Transaminases and triglycerides were measured at the Hospital Clinic Core. The collagen content was measured by staining with Sirius Red and quantified by imaging software. H&E staining was performed and NAS score evaluated. Transcriptomic analysis of genes related to liver inflammation and fibrosis were measured in commercial microarrays and by qPCR.
Results: After 4 weeks feeding with HFCD diet, early NASH was detected featuring liver steatosis, liver inflammation, hepatocellular ballooning and fibrosis. AXL inhibition with bemcentinib for 2 weeks reduced all these hepatic anomalies, including triglyceride serums levels and liver steatosis, preventing NAFLD progression. After 2 weeks of HFCD diet, mice presented fatty liver without fibrosis; however, transcriptomic analysis evidenced strong upregulation of pro-fibrotic and pro-inflammatory genes, while soluble Axl levels were already increased. Of note, one week bemcentinib administration not only reduced specific inflammatory and fibrotic genes such as *Ccr2* or *Col1a1*, but also hepatic steatosis and NAS score. In contrast, in HFF-fed mice only liver steatosis was observed, without evidence of fibrosis or inflammation nor changes in sAxl levels. Interestingly, previous and on-going clinical data show significant sAXL increase in clinical patients with only diagnosed liver steatosis, showing no histological signs of inflammation or fibrosis. These results justify

further transcriptomic patient evaluation and possible evolution depending on sAXL levels.
Conclusion: sAXL levels reveals as a potential NAFLD-NASH transition marker, indicative of the initiation of liver inflammation and fibrosis before histological detection. Early treatment with bemcentinib prevented experimental NASH appearance, pointing to AXL antagonism as possible strategy for future clinical trials.

SAT007

Efficacy and safety of an acetyl CoA carboxylase inhibitor are improved in combination with PPAR agonists in a dyslipidemic rat model

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Background and Aims: Firsocostat (FIR), a liver-directed acetyl-CoA carboxylase inhibitor (ACCi) is under investigation in NASH patients with F3/F4 fibrosis. FIR reduces hepatic steatosis and liver biochemistry in NASH patients but raises plasma triglycerides (TG) in some patients with high baseline TG. ACCi combination (combo) with fenofibrate (Feno, a peroxisomal proliferator-activated receptor (PPAR) α agonist (ag)) mitigates the plasma TG increase. Here we evaluated the safety (plasma TG reduction) and efficacy (liver TG reduction) of ACCi combo with PPAR ag with different selectivity profiles: Feno, Elafibranor (Ela, PPARα/δ ag), Seladelpar (Sela, PPARδ ag) and Lanifibranor (Lani, pan PPAR ag).
Method: Male rats were fed a fast food diet containing high fat, cholesterol and sugar for 28 days and were treated with Vehicle (Veh) or PPAR ag from Day 8–28, and ACCi from Day 15–28. ACCi alone (30 mg/kg) was compared to ACCi combo with Feno (1, 5, 15 mg/kg), Ela (1, 3, 10, 30 mg/kg), Sela (0.2, 1, 5, 15 mg/kg) and Lani (1, 3, 10, 30 mg/kg) (n = 10/dose group). Top doses of PPAR ag were determined from the literature. Plasma TG (absolute and normalized to baseline TG per animal), and hepatic TG and gene expression were assessed.
Results: PPAR ag differentially lowered plasma TG (37–54%, Feno; 43–70%, Ela; 11–52%, >1 mg/kg Sela; 12%, 30 mg/kg Lani; $p < 0.05$ vs Veh) while ACCi raised plasma TG by 43–129% ($p = 0.02$ vs Veh) after 1 week of monotherapy. While addition of ACCi slightly raised plasma TG in the combo groups, they were maintained at or below baseline in animals receiving Feno, Ela, >5 mg/kg Sela and 30 mg/kg Lani. Hepatic Apoc3 expression (PPARα target) was reduced dose-dependently with Feno (26–74%), Ela (50–97%) and Sela (<27%), and unchanged with Lani (vs Veh). ACCi lowered liver TG by 41–49% ($p < 0.05$ vs Veh). Further reductions were seen in combo arms with 15 mg/kg Feno (63% vs Veh, $p < 0.001$) and >10 mg/kg Ela (64–76% vs Veh, $p < 0.001$). Liver TG in the Lani and Sela combo arms did not improve or showed a trend to dose-dependently increase respectively, compared to ACCi alone.
Conclusion: At least one dose of all PPAR ag tested in combo with ACCi maintained plasma TG at or below baseline, mitigating the ACCi-induced rise in plasma TG. However, while Feno and Ela improved efficacy of ACCi to reduce liver TG, Lani and Sela did not alter or worsened steatosis. These studies support the use of PPARα ag to improve efficacy and safety of FIR in NASH patients.

SAT008

PBI-4050 restores liver and adipose tissue metabolic homeostasis, and decreases fibrosis in a high-fat-diet mouse model of non-alcoholic fatty liver disease

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Background and Aims: Non-Alcoholic Fatty Liver Diseases (NAFLD), characterized by fatty acid and glucose metabolism dysregulation, has become a major global health concern. PBI-4050 is a free fatty

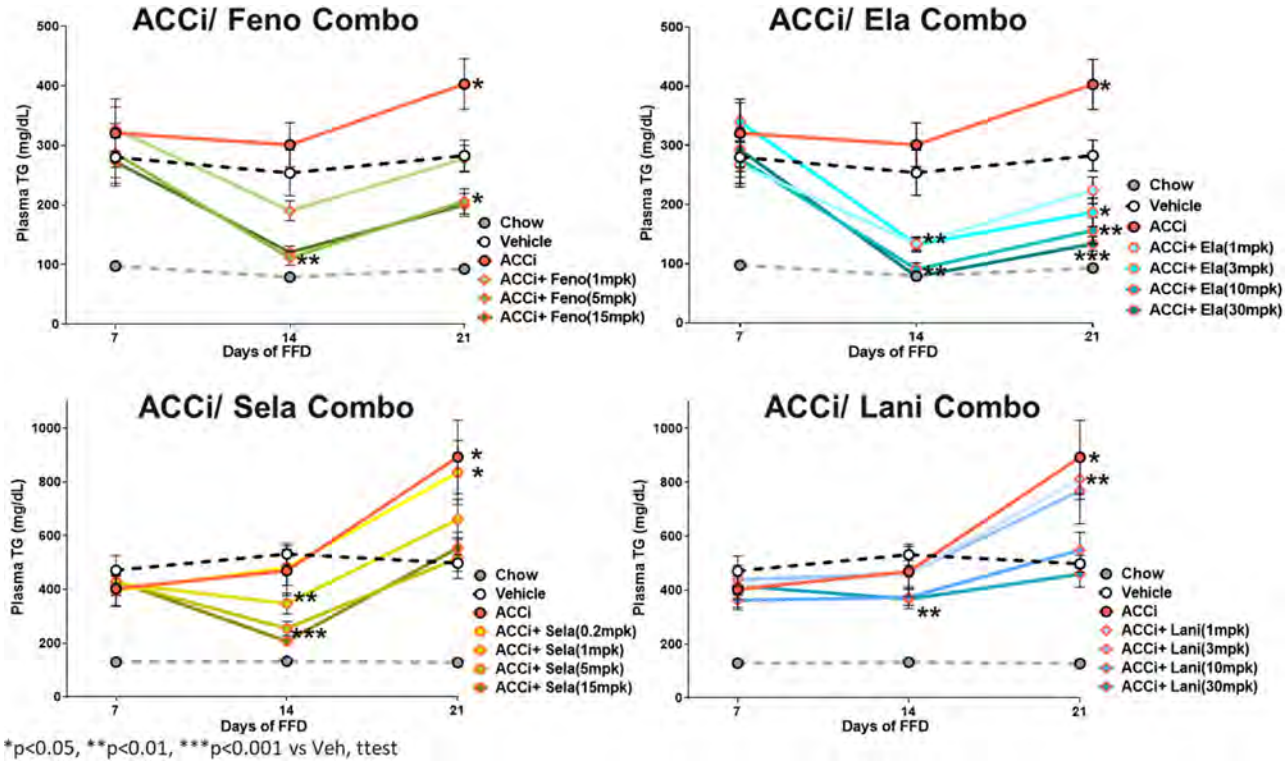

Figure: (abstract: SAT007)

acid mimetic with GPR40 agonist and GPR84 antagonist activities. It was previously shown to possess pleiotropic activities and to reduce fibrosis in different rodent models. PBI-4050 has also completed open label, non-placebo controlled, phase II clinical trials for the treatment of Idiopathic Pulmonary Fibrosis and Alström syndrome. In the present study, we used a high-fat diet (HFD) mouse model to evaluate the efficacy of this compound in preventing NAFLD progression, metabolic dysregulation, and the development of fibrosis in liver and white adipose tissue (WAT).

Method: C57BL/6 mice were fed with either a standard or a high-fat diet for 14 weeks. Mice fed with the HFD were then treated or not with PBI-4050 (200 mg/kg, oral once a day) for 6 weeks. Clinical manifestations of NAFLD, including hepatic steatosis, ballooning and inflammation, were monitored. Moreover, levels of fibrosis, a sign of NAFLD progression, were evaluated in liver and WAT. Glucose and fatty acid metabolism were also analyzed. ^{1}H-NMR hepatic metabolomic studies were used to quantify liver metabolites. Effect of PBI-4050 on mitochondrial respiration and glycolysis were measured *in vitro* in HepG2 hepatocytes using a Seahorse XF96 analyser.

Results: Histological analysis revealed that PBI-4050 treatment led to a significant reduction of hepatic steatosis, ballooning and total NAFLD score. PBI-4050 also led to a reduction in interstitial fibrosis which correlated with decreased gene levels of *Col1a1*, *Col3a1*, *Ctgf*, *Timp1* and *Mmp2*. In WAT, PBI-4050 significantly reduced immune cell infiltration and collagen deposition as well as expression of pro-fibrotic and inflammatory genes. Serum adiponectin levels were also increased by PBI-4050. Metabolomic study from liver extracts revealed that PBI-4050 restored normal levels of amino acids and energy-related metabolites that were dysregulated by HFD. Interestingly, endogenous level of glucose and ATP was decreased while NAD+ was increased by treatment with PBI-4050. mRNA expression of uncoupling proteins (*Ucp3* in liver and *Ucp1* in WAT) were also increased by PBI-4050 suggesting that PBI-4050 could affect mitochondria and increase energy expenditure. Moreover, mitochondrial oxygen consumption and acidification rate were reduced in HepG2 hepatocytes by PBI-4050 treatment *in vitro*, while in the presence of palmitate we observed an increase in fatty acid oxidation.

Conclusion: These results indicate that PBI-4050 offers the potential as a novel therapy for NAFLD, diabetes and associated metabolic syndrome.

SAT009

Adipose tissue macrophages acquire a pro-inflammatory phenotype which is associated to liver fibrogenesis in an experimental model of NAFLD in mice

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Background and Aims: Non-alcoholic fatty liver disease (NALFD) associated with obesity is characterized by a hypertrophy of adipose tissue (AT) accompanied by increased macrophage recruitment. It has been reported that pro-inflammatory mediators produced by AT macrophages (ATM) might induce hepatic inflammation in NAFLD. However, there is lack of information on the role of ATM on liver fibrosis. The aim of the present study was to elucidate the role of ATM in fibrogenesis associated to NAFLD.

Method: 15 mice were randomized into 3 groups, receiving a choline deficient supplemented with high fat diet (CDAHFD; NASH model), high fat diet (HFD) or control diet for 9 weeks. ATM and liver macrophages accumulation was quantified by using F4/80 IHC. Stromal vascular fraction enriched in macrophages was isolated from total AT and ATM phenotype and their response to pro-inflammatory mediators (INFg and LPS) was evaluated by qPCR. Hepatic fibrosis was assessed by Sirius red. Kupffer cells (KCs) were isolated using magnetic beads and its phenotype was characterized by qPCR. Primary human hepatic stellate cells (HSC) were exposed to conditioned medium of human AT from patients with obesity and fatty liver (basal and stimulated with LPS) for 24 hours.

Results: At hepatic level, NASH-mice presented a higher degree of steatosis, inflammation and fibrosis compared to animals fed with HFD or control chow. AT from NASH-mice did not display hypertrophy neither a significant infiltration of macrophages compared to HFD. However, ATMs from NASH-mice, presented a higher basal expression of pro-inflammatory cytokines and displayed an exacerbated response to pro-inflammatory stimuli mediated by CCl2. Expression levels of CCl2 in ATMs strongly correlated with the hepatic expression of fibrosis markers and with the area of collagen deposition in liver tissue samples. KC isolated from NASH mice displayed a pro-inflammatory profile with an enhanced expression of CCL2 which correlated with CCL2 levels expressed by ATMs. Finally, human AT secretome (basal and stimulated with LPS) induced activation of human HSC in-vitro.

Conclusion: In experimental NASH, ATM shows a pro-inflammatory phenotype which is associated with an increased liver inflammation and fibrogenesis and human secretome from AT activate HSC. These results suggest that modulating the pro-inflammatory phenotype of ATM might be a good strategy to mitigate inflammation and fibrosis in NAFLD.

SAT010

Intermittent hypoxia featuring the obstructive sleep apnea syndrome contributes to hepatosteatosis by upregulating the intrahepatic expression of fatty acid translocase CD36 and lipogenic genes

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) comprises varied grades of hepatic lipid accumulation, inflammation, ballooning and fibrosis; the most severe cases result in cirrhosis and liver failure. Recent evidence has linked obstructive sleep apnea syndrome (OSAS) to hepatic lipid accumulation. As OSAS is featured by periods of intermittent hypoxia (IH) during sleep, it has been suggested that IH alters hepatic lipid metabolism and could contribute to NAFLD development in OSAS patients, but little is known about the molecular mechanisms underlying increased hepatic lipid accumulation due to IH. The aim of the present study was to elucidate the molecular mechanisms by which excessive lipid accumulation occurs within the liver in conditions of IH.

Method: Histopathology and triglyceride content were assessed in livers from mice submitted to an IH protocol. Furthermore, expression of genes related to lipid synthesis (Fasn, Scd1), β-oxidation (Cpt1a, Ppara), and fatty acid uptake (Cd36) was tested by real-time PCR, Western-blot and immunohistochemistry. In addition, prevalence of NAFLD was evaluated in 90 patients with clinical and polygraphic features of OSAS and in 30 subjects with normal lung function tests by using a blood-based metabolomic assay (OWLiver test) capable to discriminate between simple steatosis, NASH and normal liver. None of patients and controls studied drank more than 20 g of alcohol per day.

Results: Grades of steatosis and triglyceride contents were significantly higher in livers from mice exposed to IH conditions than in their control littermates. Furthermore, an increased intrahepatic expression of the fatty acid translocase CD36 and lipogenic genes, such as Fasn and Scd1, was also found in hypoxic mice with respect to their normoxic controls. Noteworthy, in livers from mice submitted to IH, CD36 expression was largely restricted to the plasma membrane of hepatocytes whereas it was mainly observed within hepatocyte cytoplasms in normoxic mice. Interestingly, metabolomics profile compatible with NAFLD were significantly more frequent in OSAS patients than in subjects with normal lung function (80.7% vs 53.2%, respectively, $p < 0.05$), being NASH the most frequent metabolomic diagnosis in OSAS patients (49%).
Conclusion: NAFLD is highly prevalent among OSAS patients and IH featuring OSAS could contribute to NAFLD setup by inducing fatty acid uptake and lipid synthesis within the liver.

SAT011

The symbiotic supplementation modulate gut microbiota, regulation beta-catenin expression and prevents weight gain in ob/ob mice with non-alcoholic fatty liver disease (NAFLD)

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Background and Aims: Recent evidences suggest that symbiotic supplementation could modulate the gut microbiota, gene expression and improve metabolic disorders, including NAFLD. The aim of this study was to examine the symbiotic supplementation in ob/ob mice.
Method: 20 ob/ob mice were divided into four groups with 5 animals: Treated Obese (SBT), Control Obese (SBN), Treated Lean (SBTN) and Lean Control (SBCN). The SBT and SBTN groups received a combination of probiotics (L. acidophilus, L. rhamnosus, L. paracasei, Bifidobacterium lactis) and prebiotic (FOS) in water and standard diet for 8 weeks. The SBN and SBCN groups received water and standard diet. After 8 weeks, all animals were sacrificed, and liver and gut tissue were collected for mRNA isolation and histological analysis. SREBP1, MTTP, CPT1-α, PPAR-α, TLR4 and IL-6 gene expression were evaluated in liver tissue and beta-catenin, occluding, caderin and zonulin was evaluated in gut tissue by RT-qPCR. Microbiome DNA was extracted from stool samples and sequenced using the Ion PGM Torrent platform.
Results: The symbiotic supplementation reduced body weight gain in all treated animals (obese and lean) comparing with no treated animals (obese and lean) according the initial and final ($p = < 0.0001$; $p = 0.0012$, respectively). An increase of Cyanobacteria ($p = 0.047$), Enterobacteriaceae ($p = 0.005$) and decrease of Clostridiaceae ($p = 0.026$), Turicibacter ($p = 0.005$) and Coprococcus ($p = 0.047$) was verified in obese treated group (SBT) when compared to obese control group (SBN). A significant reduction of Sutterella bacteria ($p = 0.009$) and Turicibater ($p = 0.005$) was observed in lean treated group (SBTN) compared to lean control group (SBCN). The beta-catenin was significantly decreased in gut from obese treated group (SBT) ($p \leq 0.0001$) when compared to other groups. No changes were observed in occluding, caderin and zonulin gene expression in gut tissue as well as genes related to lipid metabolism, mitochondrial oxidation and inflammatory response in liver tissue.
Conclusion: The symbiotics supplementation prevents excessive weight gain, modulated the gut microbiota and reduces beta-catenin expression, an important gene involved in tight junction signaling, inflammation and proliferative status in NAFLD. Our results provide evidences the beneficial effects of symbiotics supplementation in NAFLD treatment.

SAT012

Treatment with the endothelin receptor inhibitor bosentan alleviates the NAFLD-associated increased intrahepatic vascular resistance and reduces steatosis and liver damage in a rat model of early NAFLD

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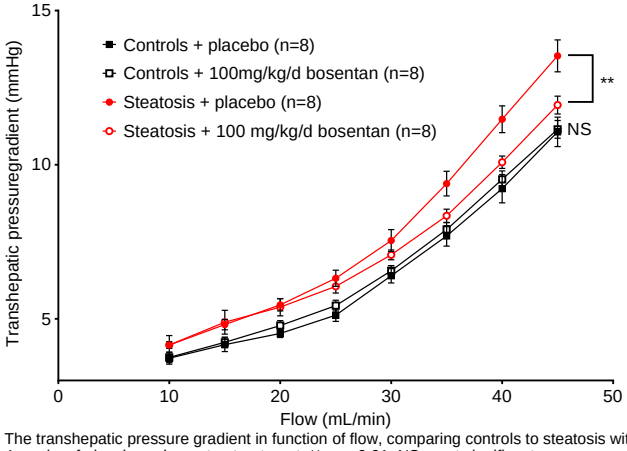
Background and Aims: The intrahepatic vascular resistance (IHVR) is increased in early non-alcoholic fatty liver disease (NAFLD), impairing hepatic blood flow and potentially causing tissue hypoxia and disease progression. We previously demonstrated that this increase in IHVR is in part mediated by vascular hypersensitivity to endothelin-1 (ET-1), which could be blocked by ET-A receptor inhibition (Van der Graaff, Hepatol 2018;68(Suppl):1011A). The aim of this study was to analyse the potential benefit of bosentan (BOS, an ET-A and -B receptor blocker) on liver haemodynamics and concurrent severity of disease in early NAFLD.
Method: The effects of ET-1 inhibition were studied in male Wistar rats (n = 8/group) fed a methionine-choline-deficient (MCD) diet, which induces severe steatosis after 4 weeks, or a control diet. Rats were daily gavaged with 100 mg/kg BOS or placebo during the complete 4 weeks of diet as preventive treatment or during the second 2 weeks of diet as curative treatment. The IHVR was studied by measuring the transhepatic pressure gradient (THPG) in an *in situ ex vivo* perfusion model at different flows (10–45 mL/min). Blood samples were collected before liver perfusion to determine ALT levels and liver tissue was harvested for histology.



The transhepatic pressure gradient in function of flow, comparing controls to steatosis with 4 weeks of placebo or bosentan treatment. ** = p<0.01, NS = not significant

Results: The basal THPG in steatotic livers confirmed the significant increase compared to controls (Fig), as previously demonstrated (Van der Graaff, Lab Invest 2018). Preventive BOS treatment significantly decreased the THPG in steatotic livers, without affecting the THPG in

controls (Fig). Moreover, despite comparable weight evolution (MCD 199.6 ± 3.5 g and MCD + BOS 200.3 ± 3.3 g at W4, p = 0.898), liver weight and liver-to-total-body-weight (TBW) ratio were lower in preventive BOS-treated (4.6 ± 0.1% liver/TBW) compared to placebo-treated rats (5.2 ± 0.3% liver/TBW, p < 0.01) with steatosis. The degree of steatosis, expressed as % fat of total liver surface, was significantly lower in preventive BOS-treated rats (from 52.2 ± 0.7% placebo to 47.1 ± 2.0% BOS, p < 0.05). ALT significantly increased in MCD fed rats (94.9 ± 14.0 U/L), whereas preventive BOS-treated rats showed ALT levels comparable to control rats (48.4 ± 3.0 U/L, p < 0.05). In curative BOS-treated rats, we observed a similar significant decrease in THPG, liver and liver/TBW ratio and ALT level. The degree of steatosis showed an insignificantly decreased trend (results not shown). In controls, none of the parameters were affected by BOS treatment.

Conclusion: BOS treatment significantly decreased the elevated THPG observed in steatosis. This effect goes along with a decrease in steatosis, lower liver weight and liver/TBW-ratio and normalisation of ALT in the absence of any effect on body weight. These findings strongly support the role of ET-1-related vascular alterations in NASH pathogenesis and its potential as a therapeutic target.

SAT013

Liver sinusoidal endothelial cell-specific RUNX-1 gene knockdown decreases hepatic inflammation and myeloid cells infiltration in pre-clinical animal models non-alcoholic steatohepatitis

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Background and Aims: Our recent studies have reported an increased expression of Runt-related transcription factor (RUNX1) in liver sinusoidal endothelial cells in patients with non-alcoholic steatohepatitis (NASH). Here, we further dissected the role of RUNX1 in NASH by in vitro and in vivo studies.

Method: In vitro, RUNX1 gene expression was downregulated in LSECs using RUNX1-siRNA followed by analysis of their angiogenic gene expression and functions by RT-PCRs and matrigel assays. In vivo, RUNX1 was silenced in LSECs in methionine choline deficient (MCD) diet-induced NASH mice by using a nanodelivery system consisting of nanolipocarrier encapsulated RUNX1-siRNA (RUNX1-NLC). After characterization of the RUNX1-NLC (both in vitro and in vivo), liver cells and liver infiltrating lymphocytes (LILs) were analyzed to study expression of RUNX1 and other angiogenic/adhesion molecules by RT-PCRs and flow cytometry. MCD mice treated only with nanolipocarriers without RUNX1 siRNA served as vehicle.

Results: Results: An in vitro knock-down of RUNX1 gene in LSECs (>50%) resulted in substantial downregulation of their angiogenic and adhesion gene expression and also angiogenic properties. In vivo, a knock-down of about 40% was achieved in the expression of RUNX1 gene in CD31+ liver endothelial cells of RUNX1-NLC treated mice, which showed a reduced expression of adhesion molecules, VCAM1 and ICAM1 in comparison to the vehicle mice. RUNX1-NLC treated mice showed marked reduction of CD45+CD3+ T cells in the liver as compared to vehicle (25.8 + 1.8 vs 39.6 + 2.5%). Also, percentages of CD11b+F4/80+ inflammatory monocytes/macrophages were significantly lower in RUNX1-NLC mice as compared to that seen in vehicle mice (5.9 + 1.1 vs 21.9 + 2.6%). A decrease in inflammatory cells in liver was also well evident in the H & E liver sections of the RUNX1-NLC mice versus vehicle animals. Hepatic TNF-α and CCL2 levels showed significant reduction in RUNX1-NLC mice in comparison to that of the vehicle mice (p < 0.05).

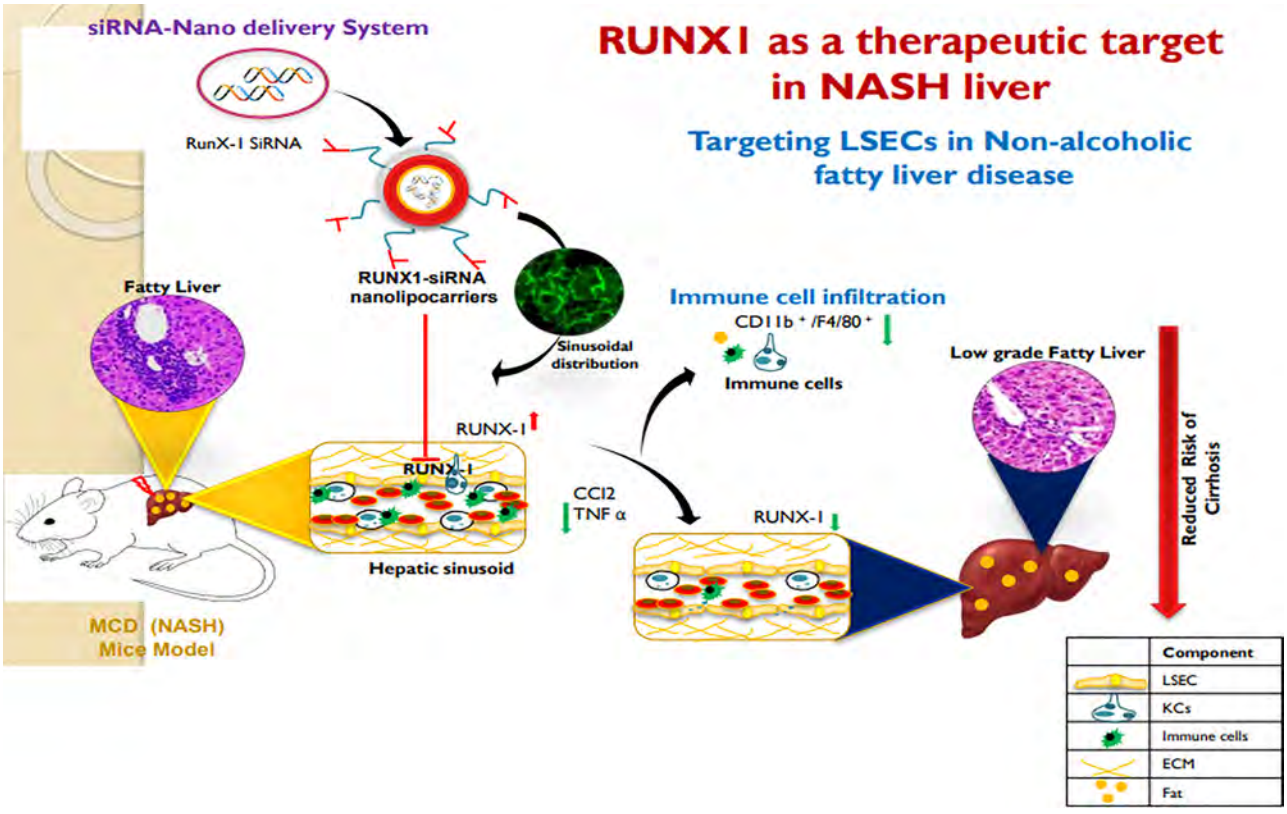

Figure: (abstract: SAT013)

Conclusion: A decrease in RUNX1 expression in LSECs reduces their expression of adhesion molecules, causing decreased infiltration of myeloid and T cells in liver, decreasing inflammation in NASH liver. The study highlights the significance of a nanodelivery system for in vivo cell-specific gene silencing and proposes it as a strategy to target LSEC-associated inflammation in NASH.

SAT014

Identification of novel biomarkers and therapeutic targets for steatohepatitis and advanced fibrosis in patients with non-alcoholic fatty liver disease (NAFLD): an in silico analysis

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Background and Aims: To integrate multiple gene expression datasets from liver biopsies to search for novel biomarkers and/or therapeutic targets for advanced fibrosis and steatohepatitis in NAFLD patients.
Method: Data was obtained from Gene Expression Omnibus or other public repositories and integrated using R studio. Expression data was quantile normalized using *RMA* (*oligo* package version 1.48.0) and *BrainArray* (version 23.0.0) probe/gene mappings to increase precision and accuracy. Probes that were not present in all arrays were excluded from the analysis. After *RMA* pre-processing, array data with a different provenance (from different studies/platforms) were cross-platform normalized (aka merged) using *Combat* method (*InSilicoMerging* package version 1.14.0) to remove batch effects. The search for biomarkers and therapeutic candidates of NASH was performed using data from six cohorts (N = 317) by pairwise comparisons between healthy individuals (n = 82) or patients with simple steatosis (n = 90) with individuals with NASH (NAS score ≥5) (n = 145). The search for advanced fibrosis markers was performed using exclusively individuals diagnosed with NAFLD (3 cohorts, N = 188) that had either mild (F0-F1, n = 152) or advanced (F3-F4, n = 36) fibrosis according to Kleiner Score. Changes in gene expression were considered significant when the FDR corrected p-value was ≤ 0.05 and the Fold Change (FC) ≥ 1.4. The behaviour of genes identified was further explored in two additional gene expression datasets that compared: 1) human primary hepatocytes exposed or not to conditions that promote inflammation and fat accumulation (0.5 mM mixture of palmitic/oleic acid + TNF-α) and; 2) Quiescent Human Primary Hepatic Stellate cells isolated from the liver of healthy patients that were exposed to conditions that promote their activation.
Results: Comparison between healthy and NASH patients showed 5 genes that changed significantly their expression: ME1 (FC: 1.53), CXCL10 (FC: 1.53), FABP4 (FC: 1.49), FST (FC: −1.45), P4HA1 (FC: −1.49). ME1 was also highly expressed in primary human hepatocytes subject to the treatment with fatty acids and TNF-α (FC: 1.53 FDR: 3.92×10^{-4}). Comparison between mild and advanced fibrosis revealed 69 genes with a significant change in their expression levels. One of these genes, which we have named as Advanced Potential Fibrosis Candidate 1 (APFC1) (FC: 1.75 FDR: 4.94×10^{-7}), has not been previously associated to advanced fibrosis and was also more expressed in activated human hepatic stellate cells compared to quiescent cells (FC: 3.72 FDR: 2.11×10^{-5}).
Conclusion: The integration of multiple expression datasets allowed us to identify a new potential candidate for advanced fibrosis in NAFLD patients, APFC1. The expression of this gene is higher in activated human hepatic stellate cells compared to quiescent cells suggesting a possible role for this gene during fibrogenesis.

SAT015

Liver-chip: a model for understanding diet-induced liver disease and drug efficacy assessment

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Background and Aims: Nonalcoholic fatty liver disease (NAFLD) is a progressive condition initially characterized by increased lipid accumulation in the liver (steatosis) and can develop into non-alcoholic steatohepatitis (NASH). There is an unmet need for a human-relevant *in vitro* model to enable successful development of therapies.
Method: To address this unmet need, we utilized our human Liver-Chip, which retains key characteristics of native liver function over long-term culture. To induce steatosis, chips were treated with saturated (palmitate) or unsaturated (oleate) fatty acids, alone or in combination. TGF-beta was used as a positive control for hepatocellular injury and stellate cell activation. To assess therapeutic efficacy against steatosis, chips were treated for two days after initiating steatosis (therapeutic), or co-treated (prophylactic) with a liver-targeted analogue of firsocostat, a known inhibitor of acetyl-CoA carboxylase (ACC - i). Morphological evaluation of the hepatocytes and AdipoRed™ staining was used to evaluate steatosis. Quantification of triglycerides released in the media was used to evaluate lipid removal, and alpha-SMA staining was used to assess stellate cell activation.
Results: We demonstrated induction of steatosis in hepatocytes in a concentration-dependent manner following continous exposure to oleate, palmitate, or in combination. Withdrawal of fatty acids significantly diminished the steatotic phenotype as well as levels of triglycerides released in accordance with relevant human *in vivo* data. Administration of TGF - beta resulted in increased stellate cell activation, hepatocellular injury, and lipid accumulation compared to the vehicle controls. Chips treated with the ACC - i demonstrated a concentration-dependent reduction in lipid accumulation in both the therapeutic and prophylactic paradigms when compared to steatosis induced controls.
Conclusion: In this study we provide preliminary data supporting the potential application of the Liver-Chip for modelling NAFLD-like phenotypes and conducting human-relevant therapeutic efficacy assessment using clinically relevant endpoints.

SAT016

AKR-001, an engineered Fc-FGF21 variant, directly modulates human liver and adipose tissue physiology, exerting beneficial metabolic, anti-inflammatory, and anti-fibrotic effects without FGFR4 agonism

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Background and Aims: Non-alcoholic steatohepatitis (NASH) is a progressive liver disease with complex etiology. Pathophysiology results from the accumulation of liver fat due to increased adipose tissue lipolysis, excess calories directed to the liver, and increased hepatic *de novo* lipogenesis. Accumulating fat drives lipotoxicity, endoplasmic reticulum stress, and oxidative stress in hepatocytes, leading to apoptosis, inflammation, and fibrosis. FGF21 acts as both an endocrine and a paracrine hormone, integrating whole body responses to nutritional changes and protecting cells against various stressors. To understand the potential for AKR-001, a clinical-stage FGF21 analog, to mitigate each of the core processes underlying NASH pathology and progression, its activity has been profiled in different human *ex vivo* tissue models relevant to NASH pathology described

above. Additionally, we sought to characterize the relative contributions of different FGF receptors to the actions of AKR-001 using a panel of endocrine FGF analogs with different FGFR selectivity profiles.

Method: Various endocrine FGF analogs have been profiled using 2D and 3D *ex vivo* human liver and adipose models, under conditions which mimic fed and fasted states by varying media glucose, insulin, and glucagon concentrations. The biological activity of different endocrine FGF analogs was characterized using transcriptomics and candidate protein expression analysis. We used a functional co-culture 3D liver model to understand direct hepatic effects of FGF21 activity on steatotic, inflammatory, and fibrotic readouts.

Results: FGF21 and AKR-001 suppress TGF-b-induced fibrogenic gene expression in a human hepatic stellate cell line. In 3D liver microtissues consisting of primary hepatocytes and various nonparenchymal cells, FGF21 and AKR-001, but not FGF19, suppress DNL and triglyceride accumulation. In this 3D human liver cell co-culture model, FGF21 and AKR-001 also suppress inflammatory activation by LPS to a greater extent than FGF19, while also suppressing fibrogenesis. Unbiased transcriptome profiling of these 3D liver microtissues, and of human adipocytes differentiated *in vitro*, demonstrated that AKR-001 recapitulates FGF21's regulation of key metabolic pathways supporting its potential for use as a therapeutic in NASH patients.

Conclusion: FGF21 and AKR-001 exert direct actions in human adipocytes, hepatocytes, and liver non-parenchymal cells consistent with suppression of steatosis, inflammatory activation, and fibrogenesis. These actions appear to be mediated by FGF21's canonical receptors FGFR1c/2c/3c, since agonism of FGFR4 does not seem to contribute additional efficacy in these tissues. This supports the appealing pharmacology of AKR-001, which has been reported to have favorable effects on markers of glycemic control and lipid metabolism and to be well-tolerated in humans.

SAT017

Propionate intervention attenuates NASH while negatively affecting cognition

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Background and Aims: There is an increasing interest to elucidate the health effects of short-chain fatty acids (SCFAs) on metabolism, obesity and brain function. Obesity is often associated with the development of non-alcoholic steatohepatitis (NASH) and cognitive impairment. We herein investigated potential health effects of the SCFA propionic acid (PA) on NASH development and brain function including cognition and behaviour readouts.

Method: During 17 weeks of run-in, LDLR−/−.Leiden mice received either high-fat diet (HFD) to establish obesity or chow as control. Obese mice were matched into groups (n = 15/group) and treated with propionic acid (PA+HFD), or a reference fatty acid (caproic acid; CA+HFD), or HFD without supplements (HFD). Cognitive and behavioral effects, as well as metabolic and inflammatory risk factors, were assessed prior to and after 12 weeks of treatment. At endpoint, liver, adipose and brain tissue were histologically and biochemically analyzed.

Results: PA, but not reference CA, reduced body weight and this effect was independent of food intake. PA also reduced fasting insulin levels and plasma cholesterol levels relative to the start of intervention. In addition, PA reduced total and subcutaneous fat mass, but did not affect WAT inflammation. Histopathological analysis of the liver demonstrated that PA reduced macrovesicular steatosis, hypertrophy and inflammation. Consistent herewith, PA reduced the inflammatory marker serum amyloid A and lowered the hepatic collagen content. PA treatment did not affect behavior in the open field test but mice showed impaired spatial memory, i.e. the latency to find the platform in the Morris water maze was increased. In line with these findings, we observed alterations in tissue integrity and gene expression in the hippocampus, a brain region important in memory consolidation. The reference fatty acid CA exerted no effects on the above readouts.

Conclusion: PA treatment during obesity had favorable metabolic effects, reducing body weight gain, improving metabolic risk factors and reducing the development of NASH and associated fibrosis. Simultaneously, PA had detrimental effects on the brain, reducing synaptogenesis signaling and affecting spatial memory. Altogether, the results from this study indicate that while the beneficial metabolic effects of PA treatment seem promising, it can also have negative effects on brain functioning and cognition, and should therefore be treated with caution.

SAT018

A shortcut from non-alcoholic fatty liver disease to HCC: c-Myc, a promising theranostic target

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Background and Aims: Non-Alcoholic Fatty Liver Disease (NAFLD) has rapidly risen as one of the leading etiologies for HCC and represents a large societal and health problem. Many factors are responsible for the high risk of NAFLD-related HCC development. Lately, oncogenes have been suggested to be determinant; however, their role still remains unknown.

Here we analysed the impact of the proto-oncogene *c-MYC* in the development of murine NAFLD and NAFLD-associated HCC.

Method: Transgenic mice bearing overexpression of c-*MYC* in hepatocytes (alb-MYC^{tg}) were studied at baseline conditions (36 weeks, 1 year) as well as after application of Western diet (WD).

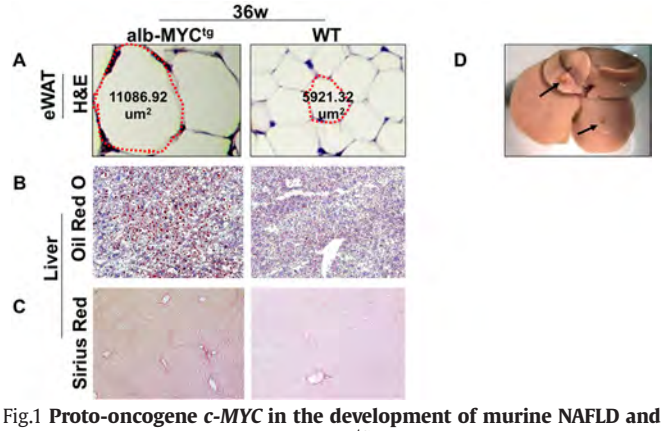

Fig.1 **Proto-oncogene *c-MYC* in the development of murine NAFLD and NAFLD-associated HCC**. (A-C) alb-MYC^{tg} mice exhibited profound spontaneous changes at 36 weeks: (A) hypertrophia of eWAT cells; (B) macrovesicular steatosis and (C) significant collagen accumulation in liver; (B) Multiple tumour nodules in alb-MYC^{tg} mice livers after 10 months of WD feeding.

Results: Mild obesity (Fig.1A), spontaneous hyperlipidaemia, glucose intolerance and insulin resistance were characteristic of 36 week-old

alb-MYC^{tg}. Moreover, alb-MYC^{tg} mice exhibited profound hepatic changes at baseline, characterized by significant macrovesicular steatosis (Fig.1B), hepatocellular ballooning and increased triglyceride content, compared to WT littermates. Liver injury and inflammation associated with elevated serum transaminases, marked infiltration of CD45 and F4/80 positive cells, increased caspase-3 activity, up-regulation of the ER-stress response and ROS production, significant collagen accumulation (Fig.1C) and compensatory proliferation were apparent in transgenic animals at 36 weeks. In agreement with earlier studies, 20% of alb-MYC^{tg} mice developed HCC at 1 year of age. Importantly, the application of WD exacerbated metabolic abnormalities, steatohepatitis, fibrogenesis and substantially enhanced the tumor incidence and tumor growth resulting in the formation of multiple tumour nodules after only 10 months of feeding in 100% of alb-MYC^{tg} mice (Fig.1D).

Conclusion: In the present study, we identified a novel function of *c-MYC* for the progression from NAFLD to HCC. It can be speculated that targeting of *c-MYC* in patients with NAFLD could reduce the risk of HCC development. However, further analysis is needed to uncover the underlying mechanisms and risk factors.

SAT019

Sex differences of adipose tissue dynamic changes in NASH progression of morbid obese patients: a preliminary study

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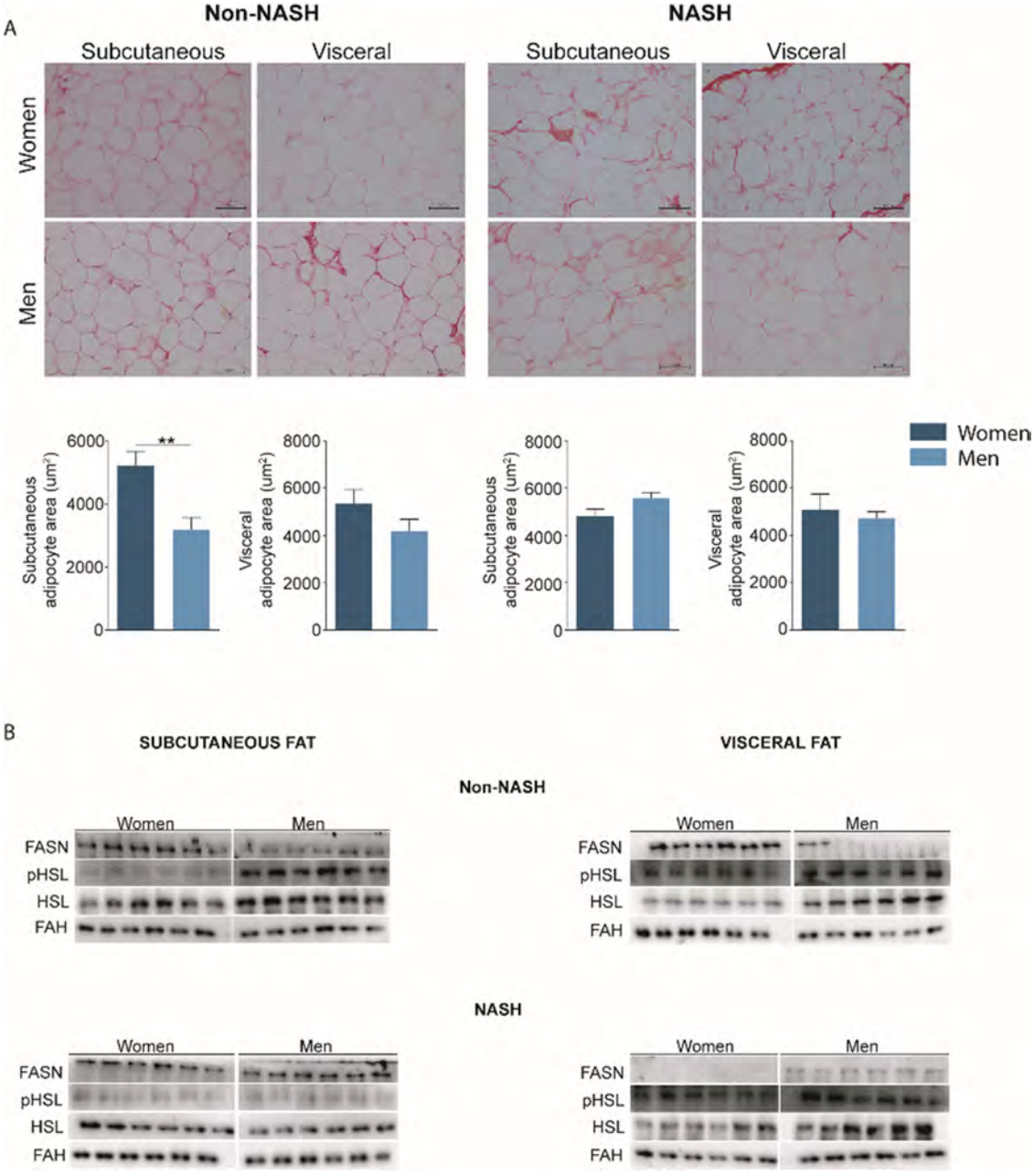

Figure: (abstract: SAT019)

Background and Aims: The prevalence of obesity has increased drastically in the last decades and this phenomenon constitutes today a serious health public problem. This obesogenic environment is characterized by an increase in adipose tissue mass. However, the adipocyte metabolism differs within (anatomical localization) and between individuals. The magnitude of adiposity is influenced by their potential growth (hypertrophy and/or hyperplasia) and their ability to triglyceride turnover. In fact, under a dysfunctional subcutaneous adipose tissue may result in the ectopic fat deposition in important metabolic organs such as visceral adipose tissue and liver. Progressively the hepatocyte loses the ability to metabolize the excess of lipids and can evoke to an inflammatory response and thereby progress to steatohepatitis (NASH). Our study aimed to assess adipose tissue metabolism and their metabolic changes during the development of NASH.
Method: Sixteen women and sixteen men with morbid obesity candidates to bariatric surgery were classified into the non-NASH group (n = 8 per sex) and NASH group (n = 8 per sex). Visceral and subcutaneous abdominal adipose tissue samples were immediately recollected before bariatric surgery. Histological analysis and immunoblot were performed to assess the adipose tissue dynamic and their impact on NASH progression according to sex.
Results: We found that in terms of hypertrophy only in Non-NASH group, the women had a significant increase in subcutaneous adipocyte size. However, the activity of adipocyte showed be heterogeneous according to the tissue and the sex. Of note, that in Non-NASH group the women showed an adipose tissue much more lipogenic in both tissues. By contrast, the adipose tissue of men showed a higher capacity to removal the triglycerides by enzymatic hydrolysis (lipolysis). Nevertheless, in the NASH group only we observed that the men visceral adipose tissue showed an increase of lipogenesis.
Conclusion: Adipose tissue is a heterogeneous organ where the adipocytes have a sex-specific metabolism and thereby the response under the same pathological condition is different.

SAT020

Hepatocyte-specific deletion of ERK5 worsens insulin resistance in a murine model of non-alcoholic fatty liver disease (NAFLD)

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Background and Aims: The extracellular signal-regulated kinase 5 (ERK5) is a member of the Mitogen-Activated Protein Kinases family highly expressed in hepatocytes, macrophages and stellate cells, and we recently generated hepatocyte-specific ERK5 knock-out mice (ERK5ΔHep). The aim of this study is to investigate the role of hepatocyte ERK5 in a murine model of NAFLD.
Method: ERK5ΔHep and control mice were fed with a high-fat diet (HFD) for 16 weeks. For glucose tolerance test (GTT) mice were injected with 1 g/kg BW glucose i.p. Insulin tolerance test (ITT) was performed by injecting 0.8 U/kg BW of regular insulin i.p. A murine hepatocyte cell line (MMH) was silenced using lentiviral vectors encoding shRNA for the ERK5 gene. Mitochondrial depolarization was assayed using the TMRE staining protocol. OXPHOS metabolism was measured by Seahorse.
Results: ERK5ΔHep mice exhibited impaired glucose tolerance and reduced insulin sensitivity in comparison to the control group. Body weight and food consumption were similar, while visceral fat was increased in ERK5ΔHep. MMH stably silenced for ERK5 showed reduced Akt activation following insulin stimulation. When cells were challenged with palmitic acid and then stimulated with insulin, Akt activation was completely abrogated in MMH/shERK5. In addition, measurement of mitochondrial membrane potential indicated a strong depolarization in MMH/shERK5 cells, which also showed an impairment of mitochondrial OXPHOS, indicating a profound impact of ERK5 deficiency on mitochondrial functions. In MMH/shERK5 cells, expression of peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α), a pivotal regulator of mitochondrial biogenesis and function, was up-regulated. Additionally, expression of TRIB3, a negative regulator of insulin signaling (through inhibition of Akt) under the control of PGC-1α was higher in MMHshERK5 cells, and its expression was further enhanced by palmitic acid. Increased expression of PGC-1α protein and TRIB3 was also observed also in liver tissues from HFD-fed ERK5ΔHep mice.
Conclusion: We have elucidated a novel pathway connecting expression of ERK5 in hepatocytes to the regulation of insulin sensitivity through PGC-1α, TRIB3, and Akt, which is relevant to the pathogenesis of NAFLD.

SAT021

MicroRNAs involved in the progression of non-alcoholic fatty liver

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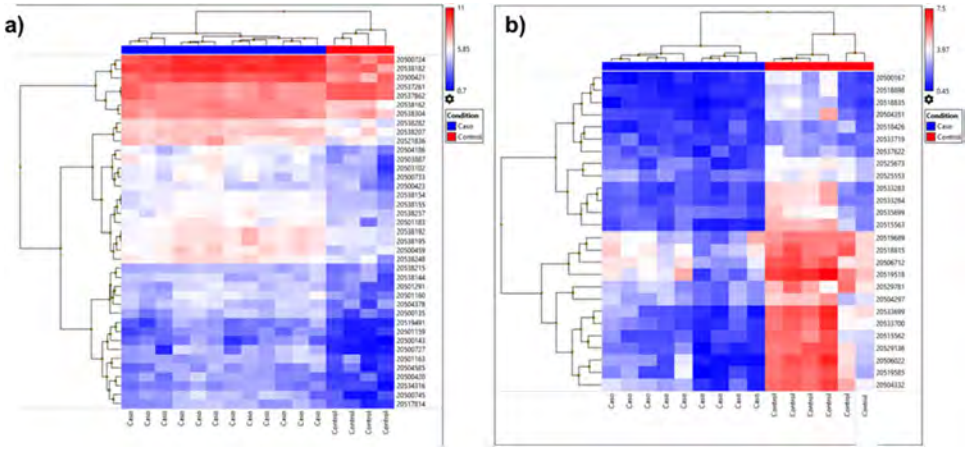

Figure: (abstract: SAT021): **Microarrays heat maps.** a) NAFLD patients compared to controls, b) NASH patients compared to controls.

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the world; its prevalence has increased recently, accompanied by global obesity pandemic. It is a complex entity that arises from numerous genetic, environmental, behavioral and social factors. Non-alcoholic steatohepatitis (NASH) is part of the disease progression and is a preamble to more severe complications such as cirrhosis and hepatocellular carcinoma. Currently, the only tool to diagnose NASH is liver biopsy. The aim is to identify the different microRNAs (miRNAs) involved in NAFLD progression.
Method: 117 patients were recruited; liver biopsy and a blood sample were obtained; 30 were submitted to microarray assays and classified according to controlled attenuation parameter (CAP) and NAFLD activity score (NAS). Patients with CAP ≤ 232 dB/m, 0-point NAS and histopathological report without alterations, were the control group; with CAP ≥ 290 dB/m, NAS with 1 to 3 points and histopathological report with steatosis in more than 5% of hepatocytes, were the NAFLD group, and patients with CAP ≥290 dB/m, NAS ≥5 points and histopathological report with steatosis accompanied by inflammatory ballooning and infiltration, were the NASH group. From blood samples, liver function tests, as well as fasting cholesterol, triglycerides, and glucose levels, were determined. RNA was extracted from liver tissue to analyze the miRNAs differential expression using the GeneChip miRNA 4.0 microarray; expression levels were compared with the Affymetrix TAC software using a fold change parameter ≥2 and ≤−2; FDR ≤ 0.05 and $p \leq 0.001$.
Results: Regarding the anthropometric characteristics, BMI had a statistical difference between control 27.8 kg/m^2, NAFLD 29.1 kg/m^2 and NASH 39.1 kg/m^2 $p \leq 0.0001$; liver function profile, circulating lipids and fasting glucose did not change. The microarray analysis revealed a differential expression of 24 miRNAs in the NAFLD group, 23 were upregulated and 1 downregulated; miR-122-3p was expressed 9 times more than the control, followed by the miR-140-5p that showed almost 6 times more expression, the miR-200a-3p was 5 times more expressed, but also the miR-148b-3p and the miR-148a-5p were 4 times more expressed than the control; while the miR-6089-2 shows 2-fold drop expression compared to the control group. While NASH results disclosed 21 differentially expressed miRNAs compared to controls, miR-297, miR-3064-5p, miR3148 and miR-7844-5p showed more than 20 times decrease expression compared to the control group.
Conclusion: The results suggest that miRNAs differential expression could be used as potential NAFLD diagnostic and progression biomarkers; however, the mechanism by which these miRNAs are involved in the pathogenesis needs further investigation.

SAT022

Simultaneous intra-operative sampling from multiple anatomical sites reveals pro-inflammatory liver homing T cells in liver, adipose tissue and peripheral blood in patients with NASH

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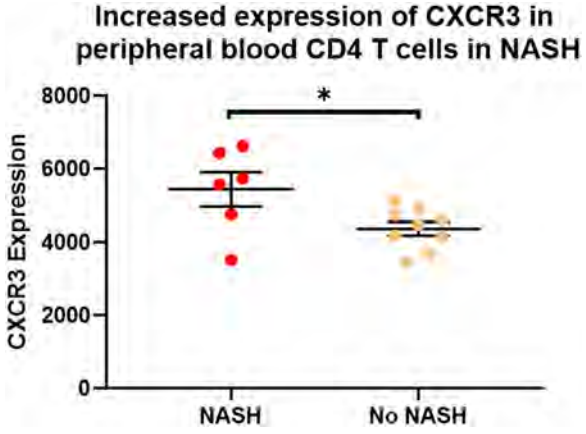
Background and Aims: Non-alcoholic steatohepatitis (NASH) is an inflammatory liver disease that can lead to fibrosis, cirrhosis and end stage liver disease. NASH has a multi-directional relationship with metabolic syndrome. Emerging evidence suggests an increase in peripheral blood T helper 1 (Th1) cells in NASH. However, the number and phenotype of T cells sampled simultaneously from adipose and liver tissue and peripheral blood in obese patients with NASH has not been studied to date. Here we test the hypothesis that a Th1 phenotype is dominant in all anatomical compartments.
Method: Patients undergoing bariatric surgery with NAFLD underwent simultaneous sampling of liver, visceral and subcutaneous adipose tissue and peripheral blood mononuclear cells for immunoprofiling by flow cytometry.
Results: We included 15 bariatric patients (median age 54); 6 with biopsy-proven NASH and 9 non-NASH. NASH patients had greater median BMI 49.8 (IQR 48.1–52.9) than non-NASH 42.0 (36.6–43.7), with mean ALT 91 vs 23 ($p < 0.001$) and median CAP score 374 dB/m vs 278 dB/m with a trend towards raised median liver elastography 11.2 Kpa (IQR 6.6–11.5) vs 7.7 Kpa (IQR 5.7–10.0). In peripheral blood, there was significantly greater CXCR3+ expression in CD4+ T cells in NASH (MFI 5447 vs 4377, $p < 0.05$) with a trend towards increased interferon gamma expression following stimulation with PMA. Overall expression of the liver homing marker CXCR6 was increased across all peripheral T cells in NASH by multiple linear regression analysis ($p = <0.05$). In particular, there were significantly more CD4 +CXCR6+ T cells in NASH versus non-NASH. Among CD45+ cells extracted from liver tissue, patients with NASH had significantly more cytotoxic CD8+ Tcells ($p = 0.01$). In the visceral adipose compartment, Th2 cells (CD4+CRTH2+) sampled from obese non-NASH patients had significantly higher levels of CXCR6 expression compared to patients with NASH. Conversely there was a trend towards higher expression of CXCR6 on Th1 cells (CD4+CXCR3+) sampled from patients with NASH compared to those without ($p = 0.059$).
Conclusion: To our knowledge, this is the first study of immune cell phenotype in multiple anatomical compartments in this patient group. We find evidence of a pro-inflammatory, liver-homing phenotype in peripheral blood and adipose tissue and a dominant type I immune phenotype in all 3 compartments. Further investigation of the role of the adaptive immune system in the pathogenesis of NASH is warranted.



SAT023

The influence of obesity, non-alcoholic steatohepatitis and bariatric surgery on plasma lipid profile

Helena Castañé[1], Anna Hernández-Aguilera[2], Montserrat Fibla Simó[2], Gerard Baiges[1], Salvador Fernández-Arroyo[2], Jordi Camps[2], Jorge Joven[2]. *[1]Universitat Rovira i Virgili, Unitat de Recerca Biomèdica, Hospital Sant Joan de Reus, Reus, Spain; [2]Institut d'Investigació Sanitària Pere Virgili, Unitat de Recerca Biomèdica, Hospital Sant Joan de Reus, Reus, Spain*
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Background and Aims: Obesity is often accompanied by non-alcoholic steatohepatitis (NASH). NASH is characterized by hepatic fibrosis, lipid accumulation and inflammation. Bariatric surgery (BS),

the gold standard treatment for obesity, has shown improvements in global health of obese individuals, but their effect on plasma lipid profile is still unknown. Our main aim was to assess changes in lipid profile of control population, obese patients with and without NASH and obese patients that undergone BS and were followed-up 12 months.

Method: Plasma samples were obtained from the participants and a lipid extraction was fulfiled. Then, we performed a lipidomic analysis by UHPLC-ESI-QTOF-MS. Results were compared in five different ways: healthy controls (n = 50) *vs* obese patients without NASH (n = 50) (obesity effect), obese patients with (n = 50) and without (n = 50) NASH (NASH effect), obese patients 12 months after BS (n = 50) *vs* obese patients with and without NASH (effect of BS in obese patients). Healthy individuals were also compared to obese patients 12 months after BS to assess possible restoration of healthy lipidome.

Results: Most lipid concentrations were statistically decreased in non-NASH obese patients than in healthy controls. Besides, obese patients with NASH had increased lipid concentrations compared to non-NASH obese patients. With that, we found few possible lipid candidates that could differentiate NASH from non-NASH, as seen in ROC curves of ChoE 18:1 and TG 50:1. However, multivariant analysis did not allow a complete distinction between groups. The effect of BS was different depending on the presence of NASH. If obese patients had NASH, BS altered much more lipid concentration than in obese patients that were non-NASH. Regarding obese patients and their follow-up after BS, we observed a different behaviour in the analysed lipid categories. Moreover, we observed that BS was not able to recover a healthy lipidome.

Conclusion: Obesity and mainly NASH are linked to a specific plasma lipidome. There are some lipids that are extremely different between obese patients with and without NASH that could lead to future non-invasive NASH biomarkers. Bariatric surgery improves clinical and biochemical characteristics of obese patients; however, it reduces plasma lipid concentrations even more than those concentrations found in healthy controls, probably due to the absorption modification after surgical intervention.

SAT024

Growth differentiation factor 11 promotes progression of non-alcoholic fatty liver disease

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Background and Aims: GDF11 (Growth Differentiation Factor 11) is a member of the TGF-beta superfamily and several recent papers implicated GDF11 as an antiaging factor. Nonetheless, its role in liver diseases is not fully clarified. Our aim was to evaluate the role of GDF11 in the progression of nonalcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH).

Method: We performed transcriptomic and lipidomic analyses in hepatoma cells treated with recombinant GDF11, to determine effected signaling pathways after GDF11 treatment. We administered recombinant GDF11 to *ob/ob* mice with NAFLD by daily intraperitoneal injection for 14 days to monitor the overall pathological changes in the liver. We also analyzed liver biopsies from a cohort of 33 morbidly obese Caucasian adults with biopsy-proven NAFLD (n = 20) or NASH (n = 13). We determined mRNA expression levels of GDF11 and other genes involved in NAFLD to NASH progression and we assessed correlations between obtained expression levels and clinico-pathological and histological features.

Results: In hepatoma cells, GDF11 treatment caused ALK5-dependent SMAD2/3 nuclear translocation, promoted accumulation of long acyl chain diacylglycerols and triacylglycerols and up-regulated TGF-beta activated genes involved in the deposition of extracellular matrix. In obese mice treated with recombinant GDF11 we observed

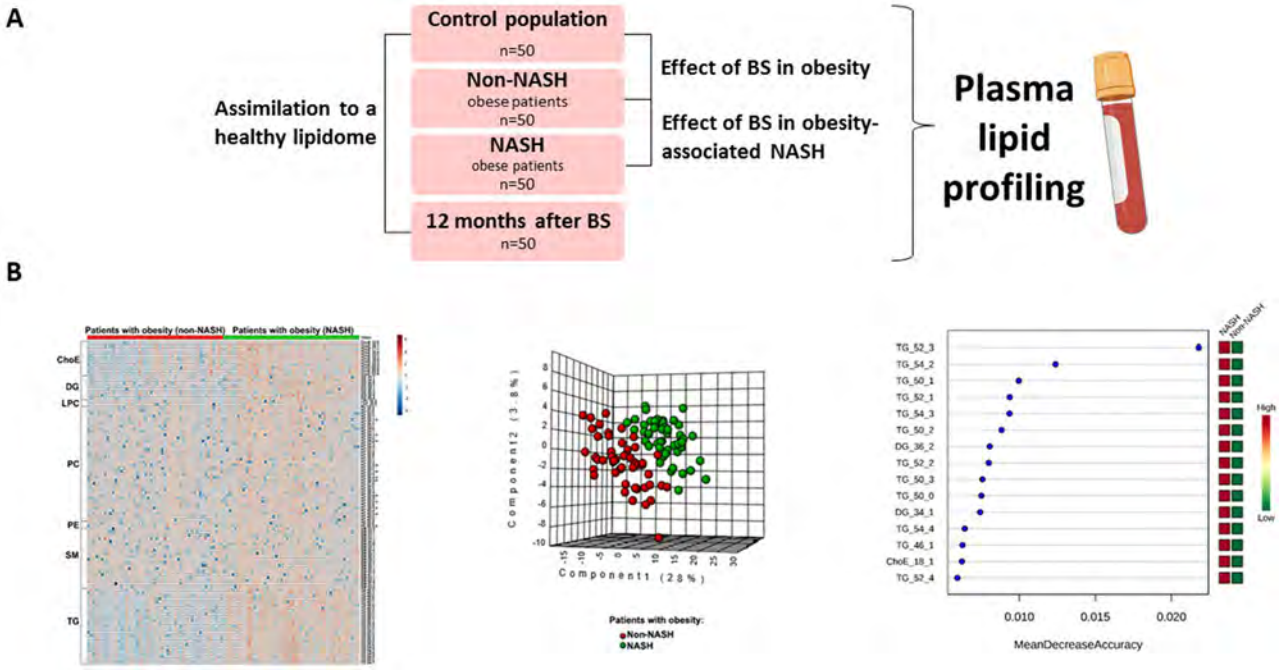
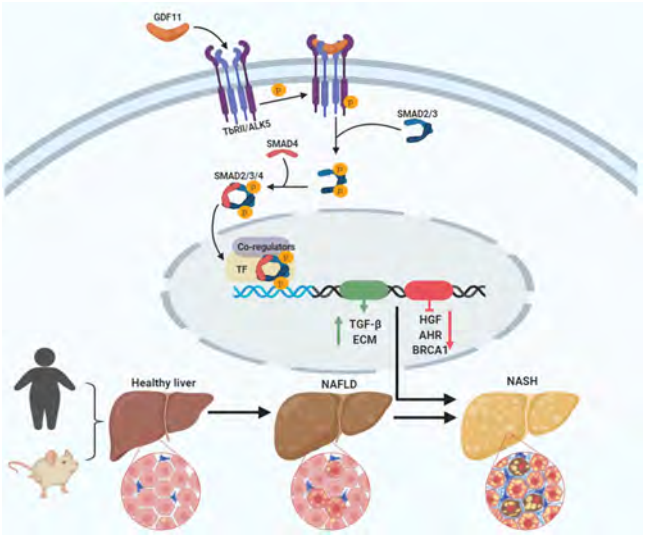


Figure: (abstract: SAT023)

exacerbated liver fibrosis without changes in total liver lipid amount and composition. GDF11 mRNA levels showed significant positive correlation with Kleiner score (NAFLD activity score) in all patients but correlations between GDF11 expression levels and those of genes CPT1, PPAR-gamma, SREBP1 and Col1A1 were significant only in morbidly obese patients with NASH (not in the NAFLD subgroup).



Conclusion: The use of GDF11 is harmful in the context of obesity dependent NAFLD as its supplementation leads to the promotion of liver fibrosis in both *in vitro* and *in vivo*. Taking into the account the high prevalence of NAFLD in the developed countries (up to 30% of the general population), caution should be taken when considering therapies based on GDF11 regulation or supplementation.

SAT025

The influence of TRPM8 variant on brown adipose tissue activity and contribution to increased susceptibility to non-alcoholic fatty liver disease among South Asians

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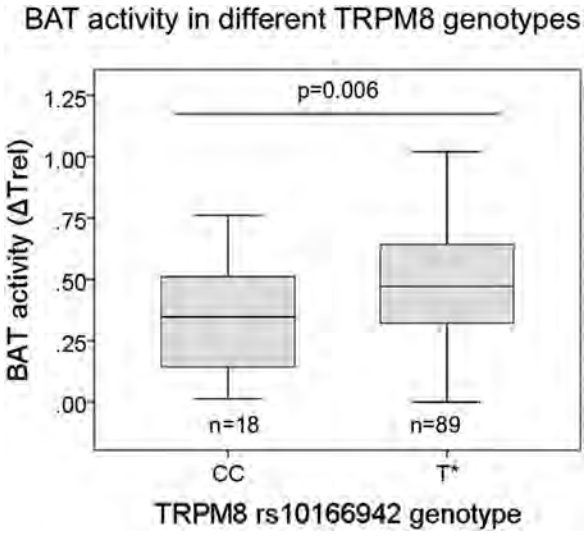
Background and Aims: South Asians are at risk of developing non-alcoholic fatty liver disease (NAFLD) and diabetes at a lower BMI than Caucasians. Brown adipose tissue (BAT) activity is linked to whole-body energy expenditure, body fat and it's associated metabolic complications. We recently demonstrated that native Indians have lower BAT activity than Caucasians. The single nucleotide polymorphism encodes a cold receptor with a putative role in physiological thermoregulation and adaption to cold environments. We hypothesise that presence of the TRPM8 variant influences BAT activity and may contribute to the susceptibility of South Asians to the metabolic syndrome including NAFLD.

Method: BAT activity was assessed in 24 native Indian (10 NAFLD, 14 control), 32 UK South Asian (17 NAFLD, 15 control) and 51 UK Caucasian (21 NAFLD, 30 control) male participants using a thermal imaging method measuring the change in temperature within the supraclavicular fossa relative to a reference point (Trel), following cold stimulus. TRPM8 rs10166942 genotyping was performed using real-time PCR.

Results: T allele frequency among Caucasians and South Asians was 0.8 and 0.48 respectively. Presence of T allele was strongly associated with increased BAT activity (0.49+/−0.22 vs 0.33+/−0.21 p = 0.006). On univariate analysis, T allele was associated with higher BMI (27.2 vs 24.7 p = 0.017), prevalent diabetes (41.6% vs 16.7% p = 0.046), but lower likelihood of NAFLD (39.3% vs 72.2% p = 0.01). Through multiple logistic regression modelling, adjusting for BMI, presence of diabetes and BAT activity, T allele was negatively associated with NAFLD (odds ratio 0.06 (0.008, 0.43; p = 0.005)).



Conclusion: Possession of the TRPM8 T allele variant is associated with increased BAT activity. Environmental factors interacting with a lower prevalence of T allele may result in reduced BAT activity among South Asians and hence, account for increased risk of NAFLD and other metabolic consequences observed in this community.

SAT026

Combinatorial effect of ezetimibe and empagliflozin in non-alcoholic fatty liver disease in a mouse model and a liver organoid for disease modeling of hepatic steatosis

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Background and Aims: Sodium-glucose cotransporter 2 inhibitor (SGLT2i) and ezetimibe, a cholesterol-lowering drug by targeting NPC1L1, have shown therapeutic potential for non-alcoholic fatty liver disease (NAFLD). SGLT2i and ezetimibe have different pharmacological mechanism, we hypothesized the combination of empagliflozin (selective SGLT2i) and ezetimibe could improve NAFLD additively

Method: We used the choline-deficient high fat diet (CD-HFD)-induced murine model of NAFLD that has key features of human metabolic syndrome. 6-week-old C57BL/6J mice were fed a CD-HFD for 8 weeks. Then these mice were divided into four groups: vehicle, ezetimibe (10 mg/kg), empagliflozin (10 mg/kg), and ezetimibe

(10 mg/kg) + empagliflozin (10 mg/kg). After 8 weeks, mice were sacrificed and subjected to blood measurements, and tissues for RNA isolation, lipid measurements and histology.
Results: Ezetimibe, empagliflozin, and combination therapy significantly reduced liver steatosis. However, the histological NAFLD activity score (NAS) was most improved in the ezetimibe/empagliflozin group (0.667) than in the ezetimibe group (2.0, P = 0.032) or empagliflozin group (3.33, P = 0.043). Hepatic lipid contents were also significantly lower in the ezetimibe/empagliflozin group compared to other groups. Hepatic expression of lipogenesis genes such as FAS (Fatty Acid Synthase), ACC1 (Acetyl-CoA carboxylase 1) were significantly decreased in the ezetimibe/empagliflozin group. For in vitro study of ezetimibe and/or empagliflozin, we utilized murine liver organoids and provided them with fatty acid to induce hepatic steatosis. Lipid accumulation was observed in liver organoids treated with fatty acid compared with control. When liver organoids with fatty acid were also treated with ezetimibe and/or empagliflozin, lipid accumulation was most diminished in the ezetimibe/empagliflozin group by measuring fluorescence intensity.
Conclusion: Our data suggested that combined administration of empagliflozin and ezetimibe can additively improve NAFLD by decreasing lipogenesis. These results provide new insight into pathogenesis and strategies for treatment of the NAFLD.

SAT027
Deviations of the peripheral blood and intrahepatic immune cell landscape between NAFLD patients and healthy controls
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Background and Aims: Multiple factors are involved in the pathogenesis of NAFLD, but the exact immunological mechanisms that cause inflammation and fibrosis of the liver remain enigmatic. Several immune cells including cytotoxic T cells, Th17 cells, regulatory T cells (Tregs), mucosal associated invariant T (MAIT) cells, γδT cells, iNKT cells and natural killer (NK) cells have been found as being altered in the lobar inflammation of NAFLD patients. However, the significance and directionality of these differences are still controversially discussed, especially with respect to human NAFLD.
Method: In this study, we present 16-color flow cytometric data of a cohort of NAFLD patients (PBMC: n = 27, liver samples: n = 15) in comparison with healthy individuals (PBMC: n = 26, liver samples: n = 3) assessing the frequency and phenotype of 23 immune cell subtypes that were correlated with clinical data.
Results: PBMC of NAFLD patients showed decreased frequencies of total CD3+, CD8+ T cells, CD56dim NK cells and MAIT cells, but elevated frequencies of CD4+ T cells and Th2 cells compared to healthy controls. IHL of NAFLD patients showed decreased frequencies of total T cells, total CD8+ T cells, Vd2+ gamma delta T cells, and CD56bright NK cells, but elevated frequencies of Vdelta2- gamma delta T cells and CD56dim NK cells compared to healthy controls. The activating receptor NKG2D was significantly less frequently expressed among iNKT cells, total NK cells and CD56dim NK cells of PBMC of NAFLD patients compared to healthy controls. More strikingly, hepatic fibrosis as measured by fibroscan elastography negatively correlated with the intrahepatic frequency of total NK cells (r^2 = 0,3737, p = 0,02). Hepatic steatosis as measured by controlled attenuation parameter (CAP) value negatively correlated with circulating NKG2D+ iNKT frequency (r^2 = 0,3365, p = 0,0047).
Conclusion: Our data provide an overview of the circulating and intrahepatic immune cell composition of NAFLD patients, and point towards a potential role of NK cells and iNKT cells in the regulation of hepatic fibrosis and steatosis in NAFLD.

SAT028
High-throughput sequencing identified MIR-193a as a potential biomarker of non-alcoholic fatty liver disease activity
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Background and Aims: The current gold standard of non-alcoholic fatty liver disease (NAFLD) diagnosis is based on histological scoring of liver biopsies. Disease activity can be graded using the NAFLD activity score (NAS), calculated as the sum of Kleiner inflammation, ballooning and steatosis scores. Liver biopsies carry inherent risks and so circulating biomarkers are needed to circumvent the requirement for such invasive procedures. MicroRNAs (miRNAs) are small (~22 nt) non-coding RNA molecules that post-transcriptionally regulate gene expression and are known to be expressed in serum. Circulating miRNAs have been characterised as diagnostic biomarkers for a range of diseases. Accordingly, we sequenced over 2,000 serum miRNAs in a discovery cohort of patients across the NAFLD spectrum to establish a profile of circulating miRNAs from which novel disease biomarkers could be identified.
Method: miRNA libraries, using 15 µl serum for each of 183 NAFLD patients and ten healthy controls, were generated by HTG EdgeSeq and sequenced by Illumina NextSeq. Limma in the R software environment was used to perform analyses on the data. Data were normalised and corrected for batch effects. MiRNAs with a mean counts per million of >=100, a log2 fold-change (logFC) of >=0.3 and an adjusted *p* value of <=0.05 were classified as differentially expressed.
Results: Seven miRNAs were differentially expressed in severe disease activity (NAS5-8) relative to mild (NAS1-4), with miR-193a being the most significant (logFC = 0.68, *p* = 3.0 × 10^−07, AUROC = 0.71). Additionally, miR-193a was the most significant (logFC = 1.5, *p* = 3.5 × 10^−10, AUROC = 0.94) of 121 differentially expressed miRNAs above a more stringent logFC threshold of >=1 in NAFLD patients relative to controls. Distilling NAFLD into steatosis and non-alcoholic steatohepatitis (NASH) with fibrosis stage (F0-F4) confirmed a consistent and significant upregulation of miR-193a in each of the classifications relative to the controls.
Conclusion: We have identified a potentially clinically significant differentially expressed circulating miRNA, which appears to primarily reflect NAFLD grade and activity. Quantification of miR-193a may facilitate non-invasive NAFLD diagnoses. This, along with other significantly differentially expressed miRNAs, is currently being validated in an independent cohort of samples using qPCR.

SAT029
Ageing causes lipid metabolism imbalance and exacerbates steatohepatitis in high-fat diet-fed mice
Kazuyoshi Kon[1], Kei Ishizuka[1], Hyeon-Cheol Lee[2], Kumiko Arai[1], Akira Uchiyama[1], Hiroo Fukada[1], Shunhei Yamashina[1], Takehiko Yokomizo[2], Kenichi Ikejima[1]. *[1]Juntendo University Graduate School of Medicine, Department of Gastroenterology, Tokyo, Japan; [2]Juntendo University Graduate School of Medicine, Department of Biochemistry, Tokyo, Japan*
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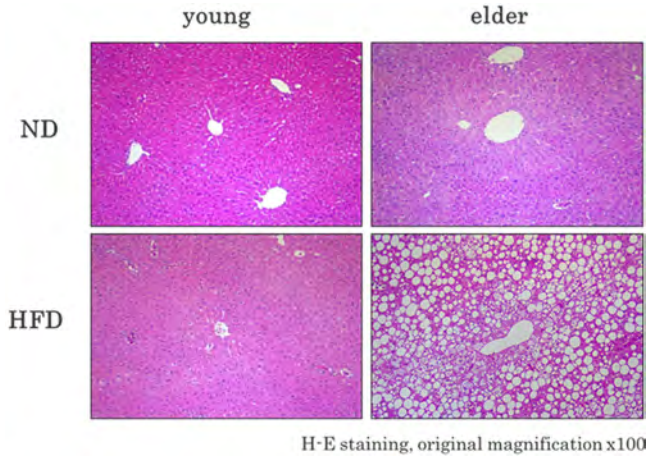
Background and Aims: Aging is an independent risk factor for the progression of nonalcoholic steatohepatitis (NASH); however, the role of aging in lipotoxicity, a major contributor to NASH, has not been fully understood. We investigated the impact of aging on lipotoxicity using aged mice.
Method: Male C57BL/6J mice aged 8 and 55 w.o. (young and elder, respectively) were fed either high-fat diet (HFD) or normal diet for 8 wks. Liver tissues were stained by immunohistochemistry for 4-hydroxynonenal (4-HNE) and Sirius-Red. Hepatic lipid composition was comprehensively analyzed using liquid chromatography coupled to tandem mass spectrometry. The expression of mRNA was determined by RT-PCR.
Results: Following HFD-feeding, elder mice developed massive steatohepatitis with hepatocyte ballooning and pericellular fibrosis, whereas young mice only developed mild steatosis (Figure). Serum ALT levels following HFD feeding were much higher in elder mice than in young mice (192 ± 17 IU/L vs. 34 ± 4 IU/L). Antioxidant enzymes such as superoxide dismutase-1, -2 and catalase mRNA were significantly decreased following a HFD in elder mice compared to young mice. In contrast, the expression of mRNA for heme oxygenase 1, tumor necrosis factor alpha, IL-6, and transforming growth factor beta following an HFD was more increased in elder mice than young mice. Higher expression of 4-HNE was also observed in elder mice fed an HFD. Lipidomics analysis revealed that HFD-feeding increased triacylglycerol and diacylglycerol predominantly containing 18:1n-9 and decreased phospholipids containing poly unsaturated fatty acid such as 22:6n-3 and 22:5n-3 in liver of elder mice compared to young mice. The HFD-induction of sterol regulatory element-binding transcription factor 1c (SREBP1c) mRNA was significantly enhanced in elder mice compared to young mice. Carnitine palmitoyltransferase IA (CPT1A) mRNA levels were increased following HFD-feeding in young mice; however, the levels were reciprocally decreased in elder mice. Peroxisome proliferator-activated receptor alpha mRNA levels were also decreased following HFD significantly in elder mice. The expression of elongation of long chain fatty acids family member 6 (ELOVL6) mRNA was equally enhanced in both young/elder mice following HFD. In contrast, fatty acid desaturase (FADS) 1 and 2 mRNA were significantly decreased in elder mice fed an HFD as compared to young mice.



H-E staining, original magnification x100

Conclusion: Elder mice developed severe steatohepatitis following diminished antioxidant enzymes as compared to young mice by same period of HFD feeding. Our findings indicated that imbalance among lipogenesis/lipolysis/lipid desaturation against HFD causes lipotoxicity by altering the lipid composition of neutral lipids and phospholipids. Correction of lipid metabolism imbalance is a potential therapeutic target for preventing exacerbation of steatohepatitis by aging.

SAT032

Anti-inflammatory and anti-fibrotic activity of TERN-201, a semicarbazide-sensitive amine oxidase inhibitor, in a rat choline-deficient high-fat diet non-alcoholic steatohepatitis model

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Background and Aims: Infiltration of leukocytes into the liver is a characteristic of non-alcoholic steatohepatitis (NASH), leading to tissue inflammation and liver injury. Semicarbazide-sensitive amine oxidase (SSAO), also known as vascular adhesion protein 1 (VAP-1), is a dual function cell adhesion molecule with a unique amine oxidase ecto-enzyme activity significantly increased in patients with NASH and independently associated with liver fibrosis stage. SSAO catalyses the oxidative deamination of aliphatic and aromatic primary amines, generating toxic products that increase systemic oxidative stress and damage the vasculature, mediating leukocyte entry into inflammatory sites. TERN-201, a novel, selective SSAO inhibitor currently in clinical development for NASH, was tested in a rat choline-deficient NASH model.
Method: Male Wistar rats were fed with a choline-deficient high fat diet (CDHFD) for 4 weeks followed by tri-weekly intraperitoneal sodium nitrite ($NaNO_2$) treatment to induce fatty liver disease and fibrosis, respectively. TERN-201 dosing was administered for 8-weeks concomitant with the start of $NaNO_2$ treatment. Serum lipids, liver enzymes and liver tissue were then analysed for changes from baseline. RNA levels of genes known to be involved in liver inflammation or fibrosis were also measured as biomarkers of drug activity.
Results: In CDHFD rats chronically treated with $NaNO_2$, treatment with TERN-201 increased the plasma concentration of methylamine indicating on-target SSAO inhibition. TERN-201 strongly reduced liver inflammation ($p < 0.001$) and gene expression associated with inflammation. Fibrosis related gene expression was also strongly reduced in the liver with TERN-201 treatment ($p < 0.005$), concomitant with a reduction in the histological fibrosis score ($p < 0.05$). TERN-201 treatment reduced GGT levels ($p < 0.05$), a marker of liver injury. As expected for an anti-inflammatory agent, TERN-201 did not induce changes in liver steatosis or serum lipids.
Conclusion: TERN-201 strongly inhibited liver inflammation in a rat model of NASH. A reduction in liver fibrosis markers was also seen, supporting the further development of this drug in patients with NASH.

SAT033

Cognitive dysfunction occurs early in experimentally induced NAFLD and is associated with systemic inflammation

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Background and Aims: A key factor now recognized in non-alcoholic fatty liver disease (NAFLD) is impaired cognition, which may affect up to 70% of NAFLD cases with significant socio-economic impacts. Chronic low-grade systemic inflammation is well described in NAFLD. The aim of this study was to address the importance of chronic low-

grade systemic inflammation in the development of cognitive dysfunction in NAFLD.

Method: Using a well-established model of NAFLD representing "western diet," 20 male Sprague Dawley rats were fed either a high-fat, high-cholesterol (HFHC) diet for 16 weeks or standard diet (10 per group). These animals were assessed for behavioural changes using previously validated neuropsychological tests, and inflammation studied through a broad panel of cytokines. Liver histology was assessed to stage NAFLD severity.

Results: The HFHC diet resulted in significant behavioural changes compared to standard diet: HFHC rats manifest a depressive affect evidenced by a significant reduction in survival behaviour ($p = 0.031$) and increased immobility ($p = 0.011$) in Porsolt's Swim Test. Moreover, the Novel Object Recognition test showed that HFHC rats displayed cognitive impairment, with impaired memory of previously encountered objects ($p = 0.047$). Chronic low-grade inflammation was confirmed in HFHC rats with significant increases in IFN-γ, GRO/KC, IL-1a, IL-2, IL-6, IL-10, IL-13, IL-17, MIP-1a, RANTES and MCP-1 (all $p < 0.05$). Histopathological assessment confirmed early NAFLD with extensive steatosis and lobular inflammation but no fibrosis in HFHC rats

Conclusion: This study shows that cognitive impairment and depression-like behaviour is present in a preclinical model of early NAFLD. These neurobehavioural changes were accompanied by chronic low-grade inflammation which may contribute to neuroinflammation, as is observed in many neurodegenerative diseases. Our observations, if extrapolated to humans, suggest a substantial disease burden and potential socio-economic impact of cognitive dysfunction in early NAFLD, even before fibrosis progression. These findings require further validation in patients.

SAT034

Thr ß-selective agonist MGL-3196 improves NAS score and plasma lipoprotein profile in the liver-humanized FRGN KO NASH model

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Background and Aims: Current preclinical rodent models of NAFLD and NASH are inadequate at predicting human clinical responses to pharmaceutical intervention because they do not show the full pathology of human disease and are incapable of modeling the role of specific genotypes known to influence disease progression within the context of human cellular signaling pathways.

Building on the liver-humanized FRGN mouse platform, we previously established an in vivo model, that recapitulates NAFLD/NASH with only high-fat diet fed to animals repopulated hepatocytes from a PNPLA3-148M homozygous donor. This I148M variant is significantly associated with a high risk of NASH development.

Method: FRGN KO mice were transplanted with human hepatocytes from a donor homozygous for the G allele on the minus strand of rs738409 in PNPLA3. After near complete repopulation of the liver with human hepatocytes, animals received a diet with 40 kcal% Fat, 20 kcal% fructose, and 2% cholesterol.

As a proof-of-concept, liver-humanized animals on HFD were treated during eight weeks with MGL-3196, a first-in-class, orally-administered, small molecule, liver-directed, thyroid hormone receptor (THR) ß-selective agonist.

Results: Both control and NASH-induced liver-humanized animals remained highly repopulated over the course of the study. Body weight and liver to body weight ratios increased in humanized mice on HFD compared to controls.

Liver-humanized mice show a lipid chemistry profile similar to humans (LDL/HDL ratio of ~1.6). After four weeks, the humanized animals on HFD had cholesterol levels significantly higher than control humanized animals. From week 8 to week 24, key NASH characteristics were increasingly detectable in the HFD fed animals: steatosis, hepatocyte ballooning, Mallory bodies, collagen deposition, and bridging fibrosis.

During the intervention study, liver-humanized FRGN KO mice were dosed with MGL-3196 for 8 weeks after inducing NASH for 8 weeks. The animals continued to receive HFD during the study.

Animals dosed with MGL-3196 showed a smaller liver compared to controls. Blood LDL was reduced by 14.3%. A 2-point reduction in NAS (NAFLD activity score) of 2.17 vs 4.25 was observed. This was mainly due to a reduction in steatosis. Fibrosis was not affected by the treatment and ranged from mild to perivenular/ pericellular (score 1 to 2).

Conclusion: FRGN KO mice repopulated with human PNPLA3-148M hepatocytes and fed HFD developed key aspects of NASH. Unlike current rodent models, the blood lipid profiles resembled those in humans with NAFLD. Histological analysis showed time-dependent progressive accumulation of typical NASH features.

As a proof-of-concept, FRGN KO mice were dosed with MGL-3196. Steatosis was reduced as shown by a significant reduction in the NAS score.

These results suggest that liver-humanized FRG KO mice fed an HFD may be a superior model for NASH.

SAT035

TM6SF2/PNPLA3/MBOAT7 loss-of function genetic variants impact on NAFLD development and progression both in patients and in in vitro models

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Background and Aims: The I148M *PNPLA3* and E167K *TM6SF2* variants alongside the rs641738 polymorphism in *MBOAT7/TMC4* locus represent the main genetic risk factors for non-alcoholic fatty liver disease (NAFLD). We previously generated a full knock-out (KO) of *MBOAT7* in HepG2 cells, homozygous for the I148M PNPLA3 (I148M MBOAT7$^{-/-}$). We aimed to 1) investigate the synergic impact of the 3 risk variants on liver injury and hepatocellular carcinoma (HCC) in NAFLD patients 2) create *in vitro* models of genetic NAFLD by silencing *TM6SF2* in I148M and I148M MBOAT7$^{-/-}$ cells.

Method: NAFLD patients (n = 1194) of whom 72 had HCC were stratified according to the presence of *PNPLA3*, *TM6SF2* and *MBOAT7* at risk variants as follows: 0 (none), 1 (1 variant in *PNPLA3*, *TM6SF2* or *MBOAT7*), 2 (2 variants) and 3 (patients carrying all the 3 variants). The additive weight of the mutations was correlated with liver disease severity. Finally, we silenced *TM6SF2* in HepG2 (I148M TM6SF2$^{-/-}$) and I148M MBOAT7$^{-/-}$ (I148M MBOAT7$^{-/-}$TM6SF2$^{-/-}$) through CRISPR/Cas9.

Results: At bivariate analysis, the co-presence of the 3 risk variants correlated with the grade of steatosis ($p < 0.0001$), lobular inflammation ($p = 0.009$), ballooning ($p = 0.004$) and fibrosis ($p < 0.0001$). At nominal logistic regression analysis adjusted for age, sex, BMI and T2D, patients carrying the 3 variants showed ~4-fold higher risk of fibrosis>2 ($p = 0.002$), cirrhosis ($p = 0.02$) and HCC ($p = 0.09$). In I148M TM6SF2$^{-/-}$ and I148M MBOAT7$^{-/-}$TM6SF2$^{-/-}$ cells, intracellular lipid droplets and TG content were higher than in I148M HepG2 ones ($p < 0.01$), and the expression of genes involved in *de novo* lipogenesis, cholesterol biosynthesis and β-oxidation was altered (p

< 0.05). Moreover, markers of endoplasmic reticulum (*XBP1*, *GRP78*) and oxidative stress, as well as lipid peroxidation and DNA damage were increased (p < 0.05). Cell injury was greater in I148M MBOAT7$^{-/-}$ TM6SF2$^{-/-}$ cells as they had the highest levels of XBP1, GRP78 and free radicals (p < 0.05). Finally, both models showed higher proliferation rate compared to control (p < 0.01), but still more in I148M MBOAT7$^{-/-}$TM6SF2$^{-/-}$ cells (p < 0.05).

Conclusion: We firstly generated an *in vitro* stable compound knockout of genetic NAFLD. The co-presence of the 3 risk variants impacts on NAFLD development and progression, in both human patients and experimental models. In particular, *TM6SF2* silencing alone or combined with I148M PNPLA3 and MBOAT7 KO contributes to hepatocellular damage and cell proliferation.

SAT036

Enhancing autophagy improves and slows the progression of non-alcoholic steatohepatitis disease

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Background and Aims: Loss of endothelial cell (LSEC) phenotype, or endothelial dysfunction (ED), has been associated with the progression from non-alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH). NASH is associated with defects in endothelial autophagy, which maintains LSEC phenotype. Spermidine (SPD) is a polyamine that activates autophagy and has beneficial effects on cardiovascular endothelium. Our hypothesis is that enhancement of autophagy with SPD could alleviate NAFLD progression.

Method: The impact of SPD treatment on autophagy and endothelial phenotype were evaluated in vitro in mouse LSEC (TSEC). Wild-type mice were pretreated with SPD (in drinking water) for two weeks and continued in a concomitant fashion with a 60% kcal fat-deficient choline diet (CDAAH, Br J Pharmacol. 2018) during 9 weeks. We evaluated autophagy levels and its impact on liver damage, ED, oxidative stress, inflammatory response and liver fibrosis.

Results: SPD activated autophagy in TSEC in vitro and in whole liver in vivo. NASH mice treated with SPD showed a decrease in adipose tissue mass as well as an improvement in basal glucose, consistent with amelioration of the metabolic phenotype. SPD had a hepato-protective effect with an improvement of ED and reduction of fibrosis degree. Changes in hepatocyte ballooning degree were observed but not in steatosis. SPD treatment reduced mitochondrial oxidative stress and activated the selective degradation of dysfunctional mitochondria (mitophagy), leading to an improvement in mitochondrial phenotype. Interestingly, SPD had also an anti-inflammatory effect in NASH mice, characterized by a deactivation of the NLRP3 inflammasome and a reduction of proinflammatory macrophage phenotype. No toxicity was observed. Finally, enhancement of autophagy by SPD improved endothelial response to oxidative stress by means of increased viability, reduced ROS production and improved mitochondrial phenotype.

Conclusion: Autophagy inducement by SPD promotes endothelial response to oxidative stress by eliminating dysfunctional mitochondria, improving ED, reducing inflammation and attenuating liver fibrosis during the progression of NASH disease and may be a new and attractive antifibrotic strategy.

SAT037

The PSRC1 rs599839 A > G variant disentangles the risk of coronary artery disease and hepatocellular carcinoma in Italian NAFLD patients

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Background and Aims: Several inherited variants that regulate hepatic lipid handling increase the susceptibility to develop nonalcoholic fatty liver disease (NAFLD) and progress to nonalcoholic steatohepatitis (NASH), fibrosis and hepatocellular carcinoma (HCC). Dyslipidemia and enhanced cardiovascular risk are typical features of NAFLD. The rs599839 A > G variant in the 3' UTR region of PSRC1, located in the CELSR2-PSRC1-SORT1 locus, has been previously associated with coronary artery disease (CAD) and reduced circulating lipids. Aim was to examine the impact of the rs599839 variant on metabolic traits and liver damage in a large histologically characterized cohort of patients at risk of NASH.

Method: We studied the impact of the rs599839 variant in 1224 Italian NAFLD patients (Liver Biopsy Cohort (LBC)), in 500,000 individuals (UK Biobank Cohort (UKBBC)) and in 366 HCC (The Cancer Genome Atlas (TCGA)). Hepatic expressions of PSRC1, SORT1 and CELSR2 genes were evaluated by RNAseq in a subset of patients (n = 125).

Results: The rs599839 G allele was associated with lower circulating LDL (beta: –0.19; 95%c.i.–0.3–0.09; p = 0.0003), higher HDL (beta: 0.07; 95%c.i. 0.03–0.10; p = 0.0008), reduced intima-media thickness (beta: -0.06; 95%c.i.–0.1–0.01; p = 0.008), decreased carotid plaques (OR: 0.23; 95%c.i. 0.04–1.3; p = 0.09) and hypertension (OR: 0.43; 95% c.i. 0.18–0.98; p = 0.04) in LBC and with the protection from dyslipidemia in UKBBC. Concerning the liver damage, G allele was associated with ballooning (beta: 0.26; 95%c.i. 0.01–0.51; p = 0.03) and HCC risk (OR: 1.92; 95%c.i. 1.06–3.50; p = 0.03; N = 72 cases) in LBC, but not in UKBBC. Carriers of G allele showed increased hepatic expression of PSRC1, SORT1 and CELSR2 (p < 0.0001). PSRC1 mRNA levels negatively correlated with those of genes involved in lipoprotein release (APOB and DGAT2) (p < 0.0001), while positively with those of genes implicated in cell proliferation (PCNA and TP53) (p < 0.0001). In TCGA, PSRC1 expression was associated with tumor stage worsening (beta: 0.40; 95%c.i. 0.05–0.27; p = 0.006), advanced histological grade (beta: 0.17; 95%c.i. 0.05–0.29; p = 0.005) and tumor extension (beta: 0.17; 95%c.i. 0.06–0.28; p = 0.003). As in LBC, PSRC1 expression negatively correlated with that of APOB and DGAT2, and positively with SORT1, CELSR2 and PCNA (p < 0.01).

Conclusion: The PSRC1 rs599839 A > G variant disentangles the risk of CAD and HCC in Italian NAFLD patients, likely by modulating PSRC1, SORT1 and CELSR2 expressions.

SAT038

The FASN inhibitor TVB-2640 is efficacious in a new 3D human liver microtissue model of NASH

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Background and Aims: Fatty acid synthase (FASN) is a central mediator of de novo lipogenesis (DNL) which converts dietary sugar into the fatty acid palmitate, a key signaling molecule and building block for long chain fatty acids. Increased hepatic DNL increases liver fat content, a hallmark of NAFLD (non alcoholic fatty liver disease). TVB-2640 is an oral, selective and reversible inhibitor of FASN. In a recent Ph1b study in men with characteristics of metabolic syndrome, with BMI's from 33 to 44, TVB-2640 dose-dependently reduced fasting hepatic DNL by up to 90%. FASN inhibitors reduce steatosis, inflammation and fibrosis in diseased livers of diet induced obese (DIO) murine NASH models. TVB-2640 is currently being tested in a Phase 2 study in patients with NASH, with a primary endpoint of liver fat content by MRI-PDFF imaging (NCT03938246).
Method: To better evaluate the mechanisms underlying the activity of FASN inhibitors in NASH we used a human liver tissue 3D model recently developed by InSphero (3D Insight Human Liver MicroTissue NASH Model (LMT). This model incorporates the critical primary human liver cell types including hepatocytes, Kupffer cells, hepatic stellate cells and hepatic endothelial cells and can be stimulated and tuned to recapitulate the continuum of NASH in 10 days. We report the testing of TVB-2640 in this model at dose levels from 30 nM to 3 uM, using the full complement of NASH inducers (fatty acids, sugars and LPS).
Results: Stimulation of LMTs with fatty acids, sugars and LPS induced changes consistent with NASH including steatosis, inflammation and fibrosis, with increased cellular triglycerides (TGs) and elevated cytokines. TVB-2640 was well tolerated with no observed toxicity. Following 5 days of treatment, TVB-2640 significantly reduced excess intracellular TGs by 57% ($p < 0.05$), compared to levels in non-NASH cultures; in contrast neither an ALK5 inhibitor (SB525334) nor a PPAR agonist (Elafibranor) reduced TGs significantly. TVB-2640 also decreased secreted IP-10 (IFNy-Inducible Protein-10) at all dose levels tested indicating decreased inflammatory signaling.
Conclusion: This model reproduces multiple hallmarks of liver tissue damage in NASH and the results recapitulate FASN inhibitor activity in DIO mouse models. The current study will evaluate additional impacts on hallmarks of NASH by further analysis of secreted markers and immunohistochemistry. The LMT model may be very useful in dissecting the mechanism of action of TVB-2640 and can be used to assess mechanism-based rationale for combinations of NASH agents.

SAT039

SERPINB3 inhibition as a novel target therapy for non-alcoholic steatohepatitis

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Background and Aims: Nonalcoholic fatty liver disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH) are increasingly relevant public health issues and their prevalence is predicted to increase in parallel with the increase of obesity and diabetes, but pharmacological treatments are still lacking. SerpinB3 is a serine protease inhibitor that progressively increases in the liver in relation to the extent of hepatic damage. In animal models of NASH, SerpinB3 transgenic mice display increased fibrosis and inflammation. 1-Piperidine Propionic Acid (PPA) has been recently identified as SerpinB3 inhibitor. The aim of this study was to evaluate the effect of PPA on NASH experimental models.
Method: Cell lines with different SerpinB3 expression have been incubated with PPA to assess its inhibitory activity. Real time cell proliferation was assessed using the xCELLigence instrument. Recombinant SerpinB3 (100 ng/ml) was also added to primary monocytes in the presence or absence of PPA. SerpinB3-transgenic and SerpinB3-KO mice and their control littermates were fed on MCD and CDAA diets to induce experimental NASH. Starting from the second and third month respectively, mice were injected daily with PPA (0,01 µg/g) and were sacrificed at week 8 (MCD diet) and 12 (CDAA diet). Liver pathology, IHC for F4/80, Sirius red staining, fibrosis and inflammation gene expression was carried out at sacrifice.
Results: In cell lines PPA was found to inhibit SerpinB3 mRNA expression in a dose dependent manner and these features were associated to a corresponding reduction of cell proliferation. In monocytes SerpinB3 induced overexpression of sCD163, a recognized marker of NASH, that was markedly inhibited by PPA. SerpinB3-KO mice showed significantly lower steatosis, inflammation and fibrosis after both dietary regimens, while opposite findings were observed in SerpinB3 transgenic mice. Treatment with PPA reverted these features, leading to liver profiles similar to controls. PPA significantly decreased gene expression of fibrosis and inflammation (alpha-SMA, IL-1beta, Collagen 1 and MCP-1) and lead to the activation of PPAR-gamma and PPAR-alpha.
Conclusion: SerpinB3 has been identified as a new druggable target for NASH and PPA proved to be an efficient compound that markedly reduces NASH through the inhibition of SerpinB3 and the activation of PPAR-gamma and alpha in the liver.

SAT040

Metabolism of human liver on a genome scale in non-alcoholic fatty liver disease

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is a major risk factor leading to chronic liver disease and type 2 diabetes. By using patient-matched liver transcriptomics and serum metabolomics data from the EPoS European NAFLD Registry cohort, we conducted genome-scale metabolic modeling (GSMM) to dissect hepatic metabolism across the full spectrum of NAFLD, from steatosis (NAFL) to NASH-cirrhosis.
Method: We compared the genome-scale metabolic networks across different stages of NAFLD together with healthy controls (HC, n = 10), with the patients divided into three groups: steatosis (n = 60), NASH (n = 139; F0: n = 4, F1 n = 28, F2: n = 53, F3: n = 54) and cirrhosis (n = 14). Based on transcriptomics data obtained from the liver biopsy of the patients enrolled in the European NAFLD Registry, genome-scale metabolic models of the liver were developed and contextualized for these conditions. GSMM, as a scaffold, connects metabolic genes (i.e., enzymes) and metabolic pathways. Moreover, genome-scale networks can be constrained with multi-'omics' datasets, and thus connect an organism's genotype to phenotype.
Results: GSMM revealed that similar metabolic functions are perturbed in NAFL and NASH, while additional metabolic processes were regulated in advanced fibrosis/cirrhosis. The primary liver processes such as glycerophospholipid metabolism, chondroitin/heparan sulfate, bile acid and fatty acid biosynthesis and oxidation

(carnitine shuttle in mitochondria) were affected. Lipid precursors for VLDL particles were upregulated in NAFL. Integrative analysis of transcriptomics and serum metabolomics data also revealed that several microbial pathways are up-regulated in NAFLD and may contribute to pathogenesis.
Conclusion: A GSMM approach has identified common and specific liver metabolic pathways across different stages of NAFLD progression. Data were cross-validated by serum metabolomics, where in addition analysis also revealed that specific microbially-produced metabolites are elevated in NAFLD as compared to controls. These results provide important insights into the changes in hepatic metabolism occurring during NAFLD/NASH pathogenesis.

SAT041

Hepatic RIPK3 signalling differentially modulates lipid metabolism and inflammation in non-alcoholic fatty liver disease

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Background and Aims: Necroptosis embodies an inflammatory cell death pathway dependent on receptor-interacting-protein kinase 3 (RIPK3) activity that may influence hepatocellular damage in non-alcoholic fatty liver disease (NAFLD). A signalling interplay between necroptosis and lipid metabolism is emerging. We aimed to evaluate the impact of RIPK3 signalling in lipid metabolism and in pathogenesis of human and experimental NAFLD.
Method: RIPK3 levels were evaluated in two independent cohorts of morbidly obese patients with biopsy-proven diagnosis of NAFLD (cohort A: n = 146; cohort B: n = 71), and correlated with clinical and biochemical parameters. C57BL/6 wild-type (WT) or RIPK3-deficient (*Rip3k*$^{-/-}$) mice were fed a choline-deficient L-amino acid-defined diet (CDAA; n = 14) or a control choline-sufficient L-amino acid-defined diet (CSAA; n = 14) for 32 and 66 weeks. Liver samples were processed for histological analysis. Relevant necroptosis, inflammation and fibrosis proteins and genes were also measured. Lipidomic analysis was performed and a profiler PCR array was used to evaluate expression of liver cancer-related genes.
Results: In cohort A, RIPK3 protein levels were increased in patients with more advanced fibrosis and higher NAS score, correlating with circulating hepatic transaminases. Similarly, RIPK3 mRNA was increased in cohort B NAFLD patients, comparing with healthy controls, correlating with the expression of collagen-1α1 and inflammatory and necroptosis-related proteins. In mice, RIPK3 deficiency ameliorated CDAA-induced inflammation and fibrosis. Intriguingly, *Rip3k*$^{-/-}$ mice displayed increased liver fat accumulation, body weight gain and circulating insulin levels, irrespective of the diet, when compared with WT mice. Lipidomics showed that deletion of RIPK3 shifted hepatic lipid species profiles, impacting on acyl chain length and saturation. In line with these metabolic changes, PPARγ was increased in the liver of *Rip3k*$^{-/-}$ mice. Finally, WT mice on the CDAA diet for 66 weeks developed preneoplastic nodules, which were reduced in *Rip3k*$^{-/-}$ mice. Indeed, microarray profiling and subsequent validation showed RIPK3 deficiency hampered tumourigenesis.
Conclusion: Hepatic RIPK3 correlates with NAFLD severity in humans and mice. RIPK3 plays an opposing role in controlling steatosis versus inflammation/carcinogenesis in CDAA-fed mice, suggesting that these two phenomena are dissociated events in NAFLD.
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SAT042

A novel FXR agonist EDP-297 exerts anti-inflammatory and hepatoprotective effects in human liver 3D microtissues and rodent NASH and liver injury models

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Background and Aims: The farnesoid X receptor (FXR) plays a central role in regulating bile acid and lipid homeostasis. In both preclinical and clinical settings, FXR agonists decrease liver steatosis and exert anti-inflammatory and anti-fibrotic effects, making FXR an attractive target for the management of non-alcoholic steatohepatitis (NASH). Here we report the identification of a novel, potent, FXR agonist EDP-297. The pharmacologic activity of EDP-297 was evaluated in multiple *in vitro* assays and further characterized in a human liver microtissue system and in rodent models of NASH and liver injury.
Method: Next generation sequencing of 3D InSight Human Liver Microtissue NASH model (InSphero, Schlieren, Switzerland) treated with vehicle or 1 μM EDP-297 for 10 days was performed for gene expression analysis. Male Sprague-Dawley rats that underwent sham or bile duct ligation (BDL) procedure (Charles River Laboratories, Wilmington, MA) were treated with vehicle or 1 mg/kg EDP-297, starting on Day 2 post surgery, for 5 days. Plasma biochemistry and cytokine levels were measured on the IDEXX Catalyst One analyzer or by Meso Scale Diagnostics assay (Rockville, MD). Male, biopsy-confirmed, AMLN diet-induced NASH mice (Gubra, Hørsholm, Denmark) were also treated with vehicle or EDP-297 for 12 weeks prior to sacrifice. Multiple markers of hepatic function and liver histology were evaluated.
Results: In a cell-based reporter assay, EDP-297 activated FXR with a half-maximal effective concentration (EC_{50}) of 0.2 nM. Expression of the bile salt export pump (*BSEP*) and other FXR target genes was induced with sub-nanomolar potency (EC_{50} = 0.72 nM) in the liver-derived cell line HepaRG. In 3D NASH microtissues, EDP-297 modulated multiple pathways associated with the pathogenesis of NASH. Specifically, decreased expression of genes encoding multiple lipogenic and inflammatory proteins was observed. Consistent with the anti-inflammatory effects observed *in vitro*, EDP-297-treated BDL rats showed significantly reduced expression of inflammatory (*Ccl2, Cxcl1)* and fibrotic genes (*Acta2*, *Col1a1)* and normalized circulating markers of liver injury, including ALT (76% reduction, $p < 0.001$), AST (83% reduction, $p < 0.001$) and GGT (76% reduction, $p < 0.001$). Histological analysis confirmed the hepatoprotective effects of EDP-297 with reduced immune cell infiltration and necrosis. Finally, EDP-297 was shown to be hepatoprotective in the dietary NASH model. Histological scoring, plasma and liver biochemistry will be discussed.
Conclusion: EDP-297 is a potent FXR agonist that exhibits hepatoprotective effects in rodent models of NASH and liver fibrosis. EDP-297 attenuates NASH-relevant pathways of steatosis, liver injury, inflammation, and apoptosis both *in vitro* and *in vivo.* These data support the further evaluation of EDP-297 for the management of NASH.

SAT044

Efficacy and safety of combination therapy with elobixibat and colestyramine for non-alcoholic steatohepatitis model mice

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Background and Aims: Bile acids synthesis is accelerated, and serum bile acid levels are elevated in NASH patients. The phase 2 study of volixibat, an inhibitor of the apical sodium-dependent bile acid transporter (ASBT), for NASH was conducted but resulted in early termination due to lack of efficacy and occurrence of adverse events. It is known that bile acids increase the intestinal permeability. We speculate that ASBT inhibition may increase the portal blood concentration of endotoxin by increased colonic permeability, which accelerates the liver injury. Another problem on ASBT inhibitor is the severe bile acid diarrhea. In fact, elobixibat, another ASBT inhibitor, has been approved for the treatment of chronic constipation. Colestyramine, a bile acid sequestrants (BAS), is used for the bile acid diarrhea. Taking together, we hypothesized that co-administration of ASBT inhibitor and BAS might be effective by both reducing the serum bile acids and improving the diarrhea. The purpose of this study was to test our hypothesis using mice model.
Method: Eight-week-old male C57BL/6J mice were randomly distributed into 5 groups: a basal diet fed mice (group B), a high-fat high-fructose high-cholesterol diet (AMLN) fed mice (group A), AMLN+ elobixibat 10 mg/kg - fed mice (group E), AMLN + colestyramine 0.5 mg/kg fed mice (group C) and AMLN + elobixibat 10 mg/kg + colestyramine 0.5 mg/kg fed mice (group EC). The drugs were administered for 4 weeks. After administration, hepatic condition, intake, defecation status, intestinal permeability and gene expression of liver and ileum were examined.
Results: The significant decrease in serum ALT by 87%, in serum total cholesterol by about 30%, in serum free fatty acid by about 40%, was observed in group EC compared to that in monotherapy groups. Significant reduction of hepatic lipids, and hepatic histological improvement were observed in EC compared to monotherapy groups as well. Intestinal permeability measured by FITC dextran showed the twofold increase in group E comparison to A, but completely ameliorated in EC. Consisting these findings, serum LBP, lipopolysaccharide binding protein, in group E and A were shown to be more than twice higher than that in B and significantly ameliorated in EC, which suggested combination therapy improved steatohepatitis not only by higher reduction of serum bile acid but also by reducing the endotoxin levels elevated by elobixibat. Interestingly expression of ileum ASBT in C was the highest among 5 groups. Significant reduction of serum concentration of primary bile acid was observed in EC compared to other groups. Watery diarrhea observed in E was completely ameliorated in EC.
Conclusion: Our findings clearly suggest ASBT inhibition in combination with BAS provide the promising therapeutic strategy for NASH with higher reduction of serum bile acid and tolerability compared to ASBT inhibitor monotherapy.

SAT045

The role of RIPK3 in non-alcoholic fatty liver disease: a multi-omics perspective

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is characterized by an excessive accumulation of triglycerides within hepatocytes, which can progress to non-alcoholic steatohepatitis (NASH). Genetic deletion of receptor-interacting protein kinase 3 (RIPK3) halts NASH development in mice fed a methionine and choline-deficient (MCD) diet, while exacerbating liver steatosis and adipose tissue inflammation in a high-fat diet model. Here, we aimed to further elucidate the role of RIPK3 in experimental NASH using a multi-omics approach.
Method: Liver samples from C57BL/6 wild-type (WT) or RIPK3-deficient (*Rip3k*$^{-/-}$) mice fed a choline-deficient L-amino acid-defined diet (CDAA; n = 14) or a control choline-sufficient L-amino acid-defined diet (CSAA; n = 14) for 32 and 66 weeks, were used for lipidomic and proteomic analysis, respectively. Lipidomic analysis was performed through ultra-high-performance liquid chromatography – mass spectrometry (UHPLC-MS). Formalin-fixed paraffin-embedded liver slices were cut by laser capture and the tissue obtained was used for protein extraction and LC-MS/MS analysis
Results: RIPK3 deletion halted NASH development in CDAA-fed mice, despite increasing liver fat accumulation in both NASH-inducing and control diets. In line to what has been shown in NAFLD patients, CDAA diet was associated with a reduced ratio between phosphatidylcholines and phosphatidylethanolamines (PC/PE), comparing with CSAA diet, in both *Rip3k*$^{-/-}$ and WT mice. Still, RIPK3 deficiency increased hepatic levels of diglycerides (DG) and triglycerides (TG) with shorter acyl chains and low unsaturation in mice fed the CSAA diet, while species with longer acyl chains and high number of double bonds were decreased in *Rip3k*$^{-/-}$ comparing to WT mice. These changes were also observed in CDAA-fed mice, although to a lesser extent, since the diet itself significantly increased TG and DG containing long and polyunsaturated fatty acids. In turn, *protein set enrichment analysis further* revealed that RIPK3 deficiency strongly modulated the levels of several proteins implicated in signalling pathways typically associated with NAFLD, including eIF2 signalling, mitochondrial dysfunction and oxidative stress response. These results were further validated by Western blot and suggest that mitochondria failure and protein translation impairment might be primal in the pathophysiology of NAFLD and important merging points between metabolism and cell fate.
Conclusion: In conclusion, RIPK3 deficiency shifts the lipidomic and proteomic landscape in a dietary NASH model. A throughout characterization of these molecular signatures will aid in pinpointing the specific mechanistic roles of RIPK3 in NAFLD pathogenesis.

SAT046

Muscle fat is higher in NAFLD, and increases with fibrosis stage - a retrospective liver biopsy controlled magnetic resonance imaging-based body composition study

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Background and Aims: Sarcopenia, or adverse muscle composition, develops almost universally in subjects with cirrhosis. There is ample literature support that sarcopenia leads to more pre-, peri-, and post-operative complications, as well as lower post-operative survival in liver transplant settings, and also negatively impacts TIPS treatment outcome. Recent research shows that muscle volume in combination with muscle fat greatly improves function correlations compared to muscle volume alone. In addition, visceral adipose tissue (VAT) is strongly associated with adverse Non-Alcoholic Fatty Liver Disease (NAFLD) comorbidities such as coronary heart disease. Our aim was to analyze a well-described cohort with chronic liver disease retrospectively with respect to ectopic fat content using volumetrically assessed magnetic resonance (MR) images in relation to fibrosis stage and etiology.

Method: Abdominal 2-point Dixon MR images were analyzed retrospectively for VAT volume normalized to height^2 (VATi) and muscle fat infiltration (MFI) of the spinal erectors. The volumetric analysis was performed using AMRA® Researcher in a region limited by the top and bottom of the L1 vertebrae. Mann-Whitney U-test was used for statistical analysis. Liver needle biopsy-based fibrosis staging (grouped by F0-2 and F3-4) and diagnosis (NAFLD versus other etiologies [e.g. HCV, AIH, PSC]) were defined as previously described [Forsgren MF et al, PLoS Comp Biol 2019].

Results: 34 subjects had NAFLD (F0-2 n = 27; F3–4 n = 7); 56 subjects had other etiologies (F0-2 n = 43; F3–4 n = 13). The NAFLD group had higher VATi (Fig 1A) than the other etiologies ($p < 0.001$), but neither group was significantly associated with fibrosis (NAFLD $p = 0.22$; other etiologies $p = 0.46$). The NAFLD group had higher MFI (Fig 1B) than the other etiologies ($p = 0.002$), MFI was higher in F3–4 compared to F0–2 in the NAFLD group ($p = 0.004$). In contrast, no difference between the two fibrosis groups was observed in the other etiologies ($p = 0.57$).

Conclusion: Visceral adiposity is elevated in NAFLD compared to other chronic liver diseases but does not significantly increase with fibrosis stage. Another key ectopic fat compartment – muscle fat – is elevated in NAFLD. Interestingly, muscle fat is further elevated in NAFLD subjects with advanced fibrosis, which could indicate sarcopenic processes. Prospective validation with whole-body MR body composition analysis may be required.

SAT047

Adoptive cell transfer of regulatory T cells causes an exacerbation of hepatic steatosis in high-fat high-fructose diet-fed mice

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Background and Aims: Non-alcoholic steatohepatitis (NASH) is a multisystem condition, involving the liver, adipose tissue, and immune system. Regulatory T (Treg) cells are a subset of T cells that exert an immune-controlling effect. We previously demonstrated a reduction of Treg cells in the visceral adipose tissue (VAT) in high-fat high-fructose diet- (HFHFD) fed mice, which was associated with more severe liver disease. To further investigate the role of VAT Treg cells in NASH, we aimed to correct this immune disruption through adoptive cell transfer (ACT) of Treg cells.

Method: Male 8-week-old C57BL/6J mice were fed a HFHFD for 20 weeks. Subsequently, $CD4^+$ $CD25^+$ Treg cells were isolated from the spleens of healthy 8 to 10-week-old C57BL/6J mice and were adoptively transferred to the HFHFD-fed mice via intraperitoneal injection. HFHFD-fed mice injected with PBS served as controls. Mice were sacrificed three days after the injection. Plasma ALT and cholesterol levels were determined. Liver and adipose tissue was assessed histologically. Cytotoxic T (Tc) cells, Treg, T helper (Th) 1 cells and Th17 cells were characterized in liver, VAT, subcutaneous adipose tissue (SAT), blood, and spleen via flow cytometry. Data are presented as median (Q1 – Q3).

Results: Compared to controls, ACT of Treg cells increased the proportion of Treg cells in SAT, but not in any of the other investigated tissues. Moreover, in ACT mice Th1 cells were decreased in SAT, liver, blood, and spleen, while Tc cells and Th17 cells were not affected. Furthermore, the ACT increased the ALT levels and the histological degree of steatosis, while not significantly affecting bodyweight, cholesterol level, or liver inflammation.

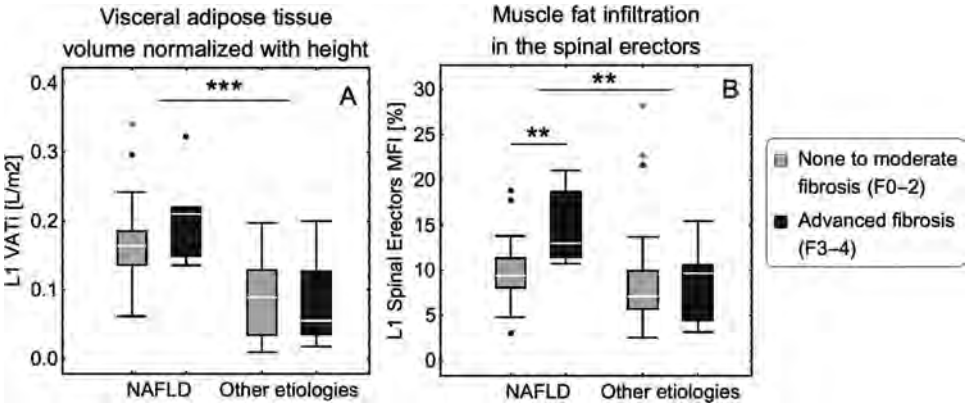

Figure: (abstract: SAT046)

Table: (abstract: SAT047)

	Control	ACT Treg cells	p-value
Liver Treg cells (% $CD4^+$ cells)	3.5 (3.5–6.7)	3.6 (1.9–7.1)	0.536
VAT Treg cells (% $CD4^+$ cells)	10.3 (7.4–12.1)	10.2 (8.0–14.1)	0.779
SAT Treg cells (% $CD4^+$ cells)	5.4 (4.3–5.8)	8.5 (7.5–10.7)	0.021
Blood Treg cells (% $CD4^+$ cells)	5.8 (5.1–9.1)	6.4 (5.9–7.9)	0.336
Spleen Treg cells (% $CD4^+$ cells)	9.9 (8.5–12.6)	11.5 (7.0–12.6)	0.662
Liver Th1 cells (% $CD4^+$ cells)	5.2 (2.6–9.0)	0.3 (0.1–3.3)	0.035
VAT Th1 cells (% $CD4^+$ cells)	2.2 (0.9–6.1)	0.7 (0.5–2.2)	0.094
SAT Th1 cells (% $CD4^+$ cells)	4.5 (2.0–6.5)	0.1 (0.7–1.1)	0.021
Blood Th1 cells (% $CD4^+$ cells)	5.4 (3.9–8.4)	2.0 (1.7–2.3)	0.021
Spleen Th1 cells (% $CD4^+$ cells)	2.2 (1.9–7.2)	0.5 (0.5–1.2)	0.026
Bodyweight (gram)	51.2 (44.3–53.9)	50.7 (48.6–53.7)	0.867
Cholesterol (mg/dL)	165 (126–173)	178 (158–188)	0.397
ALT (U/L)	12 (6–69)	77 (35–111)	0.049
Steatosis (%)	36 (31–41)	44 (42–49)	0.019
Liver inflammation (foci per mm^2)	16 (7–17)	13 (10–19)	0.715

Conclusion: Surprisingly, ACT of Treg cells in HFHFD-fed mice caused an exacerbation of hepatic steatosis. This was accompanied by an increase of Treg cells in the SAT and a general decrease in Th1 cells, while it did not correct the previously described HFHFD-induced reduction in VAT Treg cells.

SAT048

Synergic effect of a combined treatment with atorvastatin and ambrisentan in a rat model of NASH

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Background and Aims: Early stages of non-alcoholic steatohepatitis (NASH) are associated with endothelial dysfunction. The decrease in vasodilators (NO, nitric oxid) and increase in vasoconstrictors (ET-1, endotheli-1) released by sinusoidal endothelial cells (LSEC), induce hepatic stellate cells (HSC) contraction, increasing intrahepatic resistance (IHVR) and thus portal pressure (PP), even before fibrosis development. Statins have been described to increase NO synthesis in LSEC, while ambrisentan is a selective endothelin receptor A antagonist. We aimed to analyse the combined effects of atorvastatin and ambrisentan on liver hemodynamics and histology, together with assessing the contraction ability of HSC from the different study groups.
Method: Sprague-Dawley rats were fed with high fat diet with a glucose-fructose beverage (HFGFD), or control-diet (CD) for 8 weeks. Then, HFGFD animals were treated with atorvastatin (10 mg/kg/day) (HFGFD-Ato), ambrisentan (2 mg/kg/day) (HFGFD-Amb), combination of both drugs (HFGFD-AA) or remained untreated (HFDGF-Veh) for 2 more weeks. Hemodynamic parameters were registered and liver histology and serum biochemical determinations were analysed. Three-dimensional collagen lattice contraction of HSC isolated from all groups were performed.
Results: Biochemical analysis revealed a significant rise of alanine aminotransferase (ALT) levels in HFGFD animals ($p < 0.001$), indicating an alteration in hepatic function. These values were reduced to normal with all tested treatments. Atorvastatin alone was more efficient than ambrisentan improving NAS activity, although their combination showed clearly the best result reducing the number of rats with histological NASH (NAS > 3) by more than a 75%. Both atorvastatin and ambrisentan independently reduced PP (HFGFD-Veh: 10,8 mmHg vs. HFGFD-Ato: 9.42 mmHg, $p = 0.0001$; HFGFD-Amb: 9.62 mmHg, $p = 0.004$), without affecting systemic hemodynamic, but only the combined treatment was able to reduce PP to levels comparable to those of the control diet group (CD-Veh: 8.45 mmHg vs. HFGFD-AA: 9.05 mmHg). This was associated with a reduction in IHVR in the groups treated with ambrisentan either alone or in combination (HFGFD-Veh: 4.83 mmHg/mL·min·100 g vs. HFGFD-Amb: 3.69 mmHg/mL·min·100 g, $p = 0.005$; HFGFD-AA: 3.33 mmHg/mL·min·100 g, $p < 0.001$), but again, only the group treated with the combination showed indistinguishable IHVR values from those of the control group (CD-Veh: 2.86 mmHg/mL·min·100 g vs. HFGFD-AA: 3.33 mmHg/mL·min·100 g). Furthermore, HSC from the combined treatment group showed a reduced collagen lattice contraction, even under in vitro ET-1 treatment.
Conclusion: In our NASH model rats, the combination of ambrisentan and atorvastatin exerts a potent inhibition of HSC contractility, and thus intrahepatic resistance, resulting in decreased portal pressure.

SAT049

Obesity and non-alcoholic steatohepatitis: assessing lipid diversity in adipose tissue

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Background and Aims: Obesity, an increasing disease reaching pandemic proportions, is characterized by fat accumulation in adipose tissue. When adipose tissue exceeds its storage capacity, lipids reach the bloodstream and this leads to ectopic fat accumulation and inflammation in locations like the liver giving rise to non-alcoholic steatohepatitis (NASH). The aim of our study was to assess changes in histological features and in the lipid composition of visceral and subcutaneous adipose tissue (VAT and SAT) in obese patients with and without NASH.
Method: Obese patients were classified into NASH group (n = 50) and non-NASH group (n = 50). Three different comparisons were performed to analyse possible alterations in histology and lipid composition of adipose tissue during obesity and NASH development. Histological evaluation of visceral and subcutaneous fat was carried out using two stainings (Haematoxylin-Eosin and Sirius Red). To assess specific lipid signatures in VAT and SAT, a non-targeted lipidomics approach was used.
Results: Adipocyte area was higher in subcutaneous adipose tissue and in NASH obese patients. When analysing lipid differences between VAT and SAT, we observed that in general, most of the

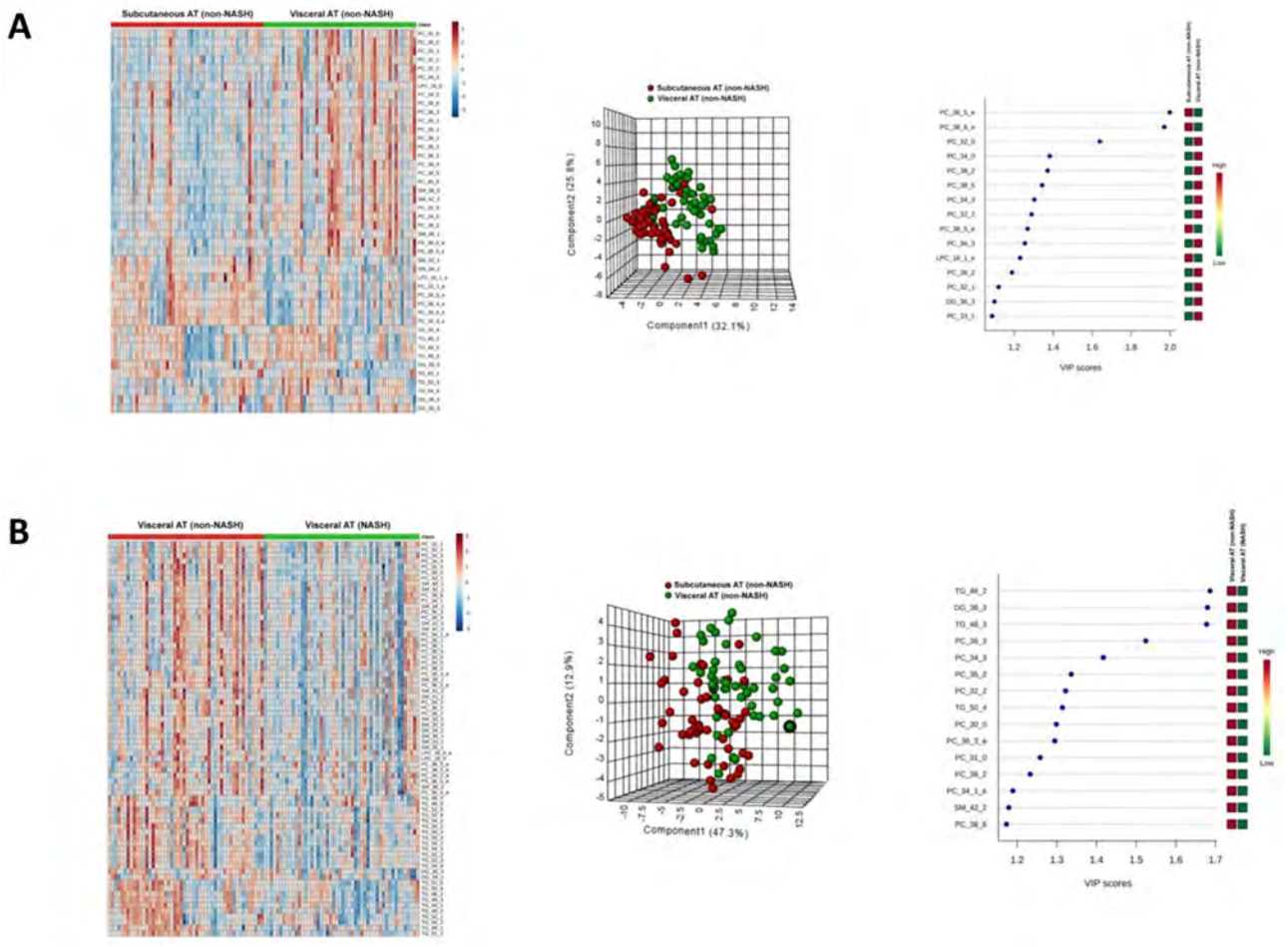

Figure: (abstract: SAT049)

significantly different lipids were increased in VAT compared to SAT of non-NASH patients (Figure 1A). When searching for NASH-specific lipid changes in VAT, we found that 68 species were significantly different and all were decreased in visceral depots of NASH obese patients compared with VAT from non-NASH patients (Figure 1B). Lastly and surprisingly, the analysis of SAT between NASH and non-NASH patients did not reveal any significant change in lipid composition.

Conclusion: Adipocyte area is higher in SAT than in VAT and is also higher in NASH group compared with non-NASH patients. Non-targeted lipidomics revealed tissue-specific lipid profiles in VAT and SAT of obese without NASH. Moreover, lipid composition of VAT was modified in NASH patients, and contrarily, SAT lipid composition was not different.

SAT051

Blocking IL-1 signaling in hepatocytes undergoing metabolic stress protects against metabolic inflammation and attenuates pro-coagulant factors

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Background and Aims: In non-alcoholic fatty liver disease (NAFLD), IL-1 signaling is induced rapidly in response to lipid overload, oxidative stress, exposure of cytokines including IL-1α/β itself, and gut-derived microbial metabolites, thereby driving sterile metabolic inflammation. The chronic inflammatory state in turn confers an increased risk of metabolic comorbidities. Aim of this study was to examine whether in vivo knockout of the IL-1 receptor type 1 (IL-1R1) on hepatocytes may prevent (extra)hepatic complications of NAFLD.

Method: 8–10-week-old male hepatocyte-specific IL-1R1 knockout (*Il1r1*$^{Hep-/-}$) mice and their wild-type (WT) littermates were fed a high-fat, high-carbohydrate diet (HFD) for 12 weeks to induce obesity-related NAFLD or a control diet.

Results: All mice fed the HFD developed a significant and comparable weight gain, hyperlipidemia, hyperglycemia, decreased adiponectin levels, and macrovesicular hepatic steatosis. Despite comparable metabolic stress induced by the HFD, levels of serum ALT, micro-vesicular hepatic steatosis, activation of c-Jun N-terminal and extracellular signal-regulated kinases (JNK, ERK) were significantly higher in the WT compared to *Il1r1*$^{Hep-/-}$ mice, suggesting attenuated liver injury. This was paralleled by an induction of peroxisome proliferator-activated receptor γ coactivator (PGC)-1α and farnesoid X receptor (FXR)-α in *Il1r1*$^{Hep-/-}$ livers, which was absent in WT mice. These findings were validated in a second model using the choline-deficient, L-amino acid-defined (CDAA) diet. Further analyses revealed that *Il1r1*$^{Hep-/-}$ mice on the HFD maintained physiological insulin sensitivity both at the level of the liver and the whole body, while WT mice exhibited impaired insulin

sensitivity (downregulation of hepatic insulin receptor and phospho-Akt expression, increased fasting insulin and HOMA-IR levels, reduced whole body-glucose tolerance testing) and increased adipose tissue inflammation, as assessed by F4/80+ macrophages, MCP-1 and IL-1RA expression. Moreover, WT mice on the HFD exhibited a clear reduction of serum thrombopoietin levels compared to *Il1r1*$^{Hep-/-}$ mice, whereas C-reactive protein was markedly increased, pointing to a suppressed pro-coagulatory state in the *Il1r1*$^{Hep-/-}$ mice.

Conclusion: This data suggests a pivotal role of hepatocyte IL-1R1 signaling in modulating whole body insulin sensitivity, metabolic inflammation and coagulation in the context of NAFLD, and supports of IL-1/IL-1R blocking approaches for the treatment of NAFLD and its comorbidities.

SAT052

Monocyte chemoattractant protein-induced protein 1 level negatively correlates with steatosis in fatty liver patients

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Background and Aims: Monocyte chemoattractant protein-1-induced protein-1 (MCPIP1) is an endonuclease that degrades selected mRNAs, viral RNAs and pre-miRNAs. The main function of MCPIP1 is a negative regulation of inflammation, through degradation of proinflammatory cytokines transcripts like IL-6 or IL-1beta. MCPIP1 inhibits also adipogenesis by degradation of C/EBPbeta mRNA and adipogenesis-related miRNA, however its role in the regulation of hepatic lipid homeostasis is unknown. Nonalcoholic fatty liver disease (NAFLD) is an umbrella term for a range of liver conditions affecting people who drink little to no alcohol. In the first stage, NAFLD is characterized by simple hepatic steatosis, that might eventually progress to nonalcoholic steatohepatitis, fibrosis, cirrhosis or hepatocellular carcinoma. The aim of this study was to analyze MCPIP1 level in liver biopsies and PBMCs of patients' who underwent bariatric surgery.

Method: For our study we enrolled 37 obese patients, excluding subjects infected with hepatitis viruses or drinking alcohol (more than 20 g and 30 g of ethanol per day for women and men, respectively). We have tested blood morphology, level of plasma components (i.e. CRP, lipid profile, liver enzymes) and amount of MCPIP1 protein in PBMC and liver samples. Liver histology analysis was performed to assess the level of steatosis (Oil Red O stain), fibrosis (Picrosirius Red) and inflammation (H&E).

Results: Body mass index (BMI) of 37 NAFLD patients enrolled to our study ranged from 38 to 58, liver steatosis was from 5% to 80% and NAFLD activity score from 3 to 7. We detected no changes in total protein, albumin nor ions (Na+, K+, Fe2+) concentrations in plasma samples. Similarly, lipid profile (total cholesterol, HDL, LDL and triglycerides) was within physiological range. CRP was above normal range in all subjects (9.14–87.59 mg/L, median 26.67 mg/L) and 90% of them had elevated levels of ALT and AST. We detected a nine fold variation of *ZC3H12A* gene expression in PBMC that resulted in negative correlation between MCPIP1 protein level with patients' BMI ($p = 0.01$). Additionally, MCPIP1 protein level in liver biopsies negatively correlated with steatosis ($p = 0.037$).

Conclusion: We demonstrated a negative correlation between MCPIP1 protein and NAFLD progression both in liver and PBMC. Thus, MCPIP1 can be considered as a new important player involved in the fatty liver progression.

SAT053

Ultrastructural changes in perfusion-fixed human non-alcoholic fatty liver disease biopsies

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is a widespread liver disease in Western society, but its multifactorial pathogenesis is not completely clear. Ultrastructural analysis of the liver showed defenestration (i.e. loss of fenestrae) of liver sinusoidal endothelial cells (LSECs) early in the course of NAFLD, promoting steatosis in animal models and *in vitro* studies. However, human data, especially on LSECs and their fenestrae, are scarce.

Applying recently developed methods for perfusion-type fixation in human samples, we aimed to explore ultrastructural changes in human liver biopsies of NAFLD patients with and without NASH, focussing on LSECs and their fenestration.

Method: We applied jet and injection fixation to needle and wedge liver biopsies of patients with NAFLD, as confirmed by routine pathologist's light microscopic (LM) diagnosis. A total of 39 samples were eligible for inclusion.

Results: In total, 37 samples were of sufficient quality for further analysis. Twelve of these had NASH (32.4%) based on the SAF (Steatosis, Activity, Fibrosis) score by LM. Comparing NASH with noNASH samples, significantly less defenestration and sinusoidal lipid embolisms were found in the NASH group (both $p < 0.05$). Other features, *i.e.* fenestrae size, presence of parenchymal and Kupffer cell lipolysosomes and megamitochondria did not differ between groups. Furthermore, newly described structures *i.e.* single cell steatonecrosis (SCSN) and inflammatory fat follicle (IFF) were seen in both groups.

Conclusion: This study showed that defenestration was more common in noNASH compared to NASH. Defenestration was not related to the degree of steatosis or fibrosis. We speculate whether this could be a protective mechanism in simple steatosis which is lacking in NASH. Sinusoidal lipid embolisms seen in the noNASH group and single cell steatonecrosis and inflammatory fat follicle seen in both groups suggest a feature of lipid overload in NAFLD.

SAT054

mIR-21 is increased in patients with NASH-associated HCC and contributes to hepatocarcinogenesis in mice with NAFLD

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Background and Aims: Molecular mechanisms governing the progression of NASH towards HCC remain elusive. We have recently shown that concomitant miR-21 ablation and FXR activation prevent NASH development in mice. Here, we aimed to evaluate the role of miR-21-dependent signalling in NASH-associated carcinogenesis.
Method: miR-21 expression was evaluated in liver biopsies and surgically resected tumors from two independent patient cohorts, which included obese patients with NAFLD (n = 200; SS cohort), HCC (n = 362) and NASH-associated HCC (n = 19) (TCGA cohort). WT and miR-21 KO mice were fed either a choline-sufficient, amino acid-defined control diet (CSAA; n = 28) or a choline-deficient, amino acid-defined diet (CDAA; n = 28) for 32 and 66 weeks. Liver samples were processed for histological analysis. miR-21 and dowstream targets, pro-inflammatory/pro-fibrogenic cytokines and metabolic relevant genes were also measured. A profiler PCR array was used to evaluate expression of liver cancer-related genes.
Results: In patients, miR-21 expression increased with NAFLD severity (steatosis, lobular inflammation, ballooning, fibrosis and the NAS score) in the SS cohort. Levels of miR-21 were markedly increased in the tumour tissue of both HCC and NASH-HCC patients compared with surrounding liver (TCGA cohort), and correlated with histological HCC markers (AFP, GPC3), disease stage and worse overall survival. WT mice fed the CDAA diet for 32 weeks developed NASH and fibrosis while CDAA-fed miR-21 KO mice exhibited increased activation of PPAR target genes and augmented mitochondrial activity. After 66 weeks, all WT mice on the CDAA diet had developed at least one preneoplastic nodule (~5.2 nodules/animal), with one animal developing trabecular HCC. miR-21 expression was significantly increased in CDAA-fed mice and further increased in HCC, concomitantly with decreased expression of PPAR. Livers presented hyperplastic foci, anisokaryosis as well as phenotypically altered and highly proliferative hepatocytes. Increased levels of pro-inflammatory/fibrogenic markers were particularly evident in pre-neoplastic liver tissues, alongside activation of oncogenic pathways. Strikingly, CDAA-fed miR-21 KO mice displayed serum ALT levels similar to control animals. The NAS score (<5), number of liver nodules (~2.3 nodules/animal), hepatocyte profliferation and expression of pro-inflammatory/fibrogenic markers and oncogenes were all significantly reduced, comparing with CDAA WT-fed mice.
Conclusion: Activation of miR-21-dependent pathways appears to contribute to NAFLD progression up to NASH-associated carcinogenesis, with its inhibiton halting HCC development. Targeting miR-21 may constitute an appealing therapeutic approach to ameilorate NASH and its progression towards HCC. (PTDC/MED-PAT/31882/2017, FCT, PT and EU H2020 Marie Sklodowska-Curie 722619 grant).

SAT055

Inhibition of autotaxin-lysophosphatidic acid signaling pathway by a novel autotaxin inhibitor FP10.47 ameliorates non-alcoholic steatohepatitis in vivo

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is a growing cause of mortality worldwide. Due to the increasing incidence of obesity and diabetes, prevalence of NAFLD is rising exponentially. 30% of affected people develop non-alcoholic steatohepatitis (NASH) that further progresses to cirrhosis and hepatocellular carcinoma. Currently, there is an unmet need for the effective therapy for the treatment of NASH. Recently, upregulated serum levels of lysophosphatidic acid (LPA) and of autotaxin (ATX, ENPP2), the enzyme that generates LPA *in vivo* have been identified in NASH, suggesting the implication of the ATX-LPA axis in NASH progression. Hence, we hypothesized that the inhibition of the ATX-LPA signaling pathway might be a promising approach to attenuate NASH. The aim of this study is to investigate the therapeutic efficacy of a novel small molecule type IV ATX inhibitor FP10.47 in NASH.
Method: ATX gene and protein expression was examined in human diseased livers and *in vivo* in mouse models. *In vitro* effectivity of ATX

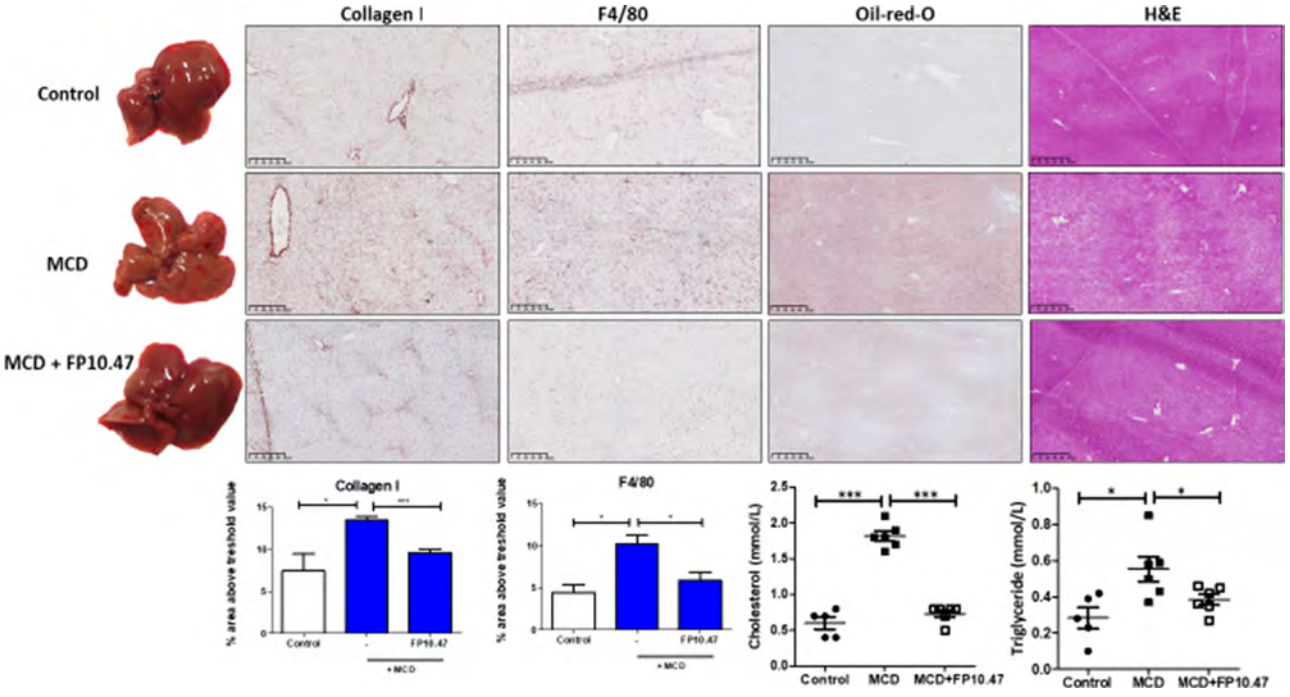

Figure: (abstract: SAT055)

inhibitor FP10.47 on fibrotic parameters, contractility and wound healing was evaluated in TGFβ-activated human HSCs. Furthermore, effects of FP10.47 on inflammatory parameters and migration was examined in M1-activated murine macrophages. Finally, FP10.47 was extensively investigated in a methionine-choline-deficient (MCD) diet-induced NASH mouse model.

Results: Upregulation of ATX expression was observed in human diseased livers with different etiologies and in murine models of NASH and alcoholic steatohepatitis (ASH). FP10.47 (1 μM) inhibited TGFβ-induced HSCs activation, contractility and migration. LPS/IFNγ-induced macrophage activation and migration was also reduced by FP10.47 (1 μM). Effects of FP10.47 were mediated via inhibition of the pERK1/2 signaling pathway. Importantly, FP10.47 didn't induce any toxicity in HSCs and macrophages. *In vivo*, in a NASH mouse model, post-disease intraperitoneal treatment with FP10.47 (5 mg/kg) strongly attenuated fibrosis, steatosis and inflammation, as observed histologically, and in gene expression profiles. Importantly, FP10.47 reduced total ALT, AST, cholesterol and triglyceride plasma levels.

Conclusion: The ATX-LPA pathway is a novel player in the pathogenesis of NASH, and inhibition of ATX is a promising therapeutic approach for the treatment of this disease.

SAT056

Recombinant glutamine synthetase reduces ammonia and hepatic fibrosis in in vitro and in vivo models of non-alchoholic fatty liver disease

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Background and Aims: The severity of fibrosis predicts risk of death in NAFLD. A causal association exists between hyperammonaemia and fibrosis in NAFLD. This occurs due to a stepwise reduction in expression and activity of urea cycle enzymes resulting in stellate cell activation and fibrosis. In NAFLD, hepatic glutamine synthase (GS) loses zonation and its activity is reduced. As GS can detoxify ammonia and also synthesise glutamine, which is important for gut and immune homeostasis, we aimed to determine whether replacing recombinant GS (AM-535), would reduce ammonia and hepatic fibrosis in NAFLD models.

Method: *In vitro precision cut liver slices (PCLS) model:* C57BL mice PCLS (n = 4/group) were administered a lipid mixture (50 μl; containing oleic, palmitic, linoleic and elaidic acid (final [2 mM]), and treated daily for 3-days with AM-535 (20 μg) in presence and absence of NH_4Cl (100 μm). *In vivo models*: (A) *Methionine choline deficient (MCD)* was administered to C57BL mice (5 g/25 g mice, n = 16) and treated with vehicle or AM 535 i.p. (30 mg/kg; 2x/w for 2w). Study was terminated at 3w. (B) *High fat high cholesterol diet (HFHC):* SD rats were fed with HFHC diet for 16w (25 g/250 g rat; n = 8), or normal chow (n = 4). HFHC rats were administered AM-535 i.p. (30 mg/kg, 2x/w) or vehicle from 8w and were terminated at 16w. Plasma ammonia levels, liver biochemistry, hepatic GS expression and severity of liver fibrosis were determined.

Results: *PCLS model:* A significant reduction in supernatant ammonia concentrations were observed from 357.5 ± 4.36 to 295.0 ± 12.91 μmol/L ($p < 0.05$) in the AM-535 treated group. *MCD model:* Ammonia concentration was significantly higher in the MCD animals compared with the chow fed animals and this was significantly reduced by AM-535 [(160.8 ± 74.3 vs 42.33 ± 16.4 μmol/L ($p < 0.05$)]. *HFHC model:* The collagen proportionate area (CPA) was significantly higher in untreated HFHC rats compared to naïve controls (4.38% vs 2.25%) ($p < 0.05$), which was reduced significantly in the AM-535 animals (CPA: HFHC vehicle: 4.38% vs 2.58%; HFHC AM-535: $p < 0.05$). In both models, hepatic immunohistochemistry for GS showed typical perivenular localisation of the administered AM-535 (Figure 1).

Conclusion: This study shows for the first time that administration of recombinant GS, AM-535 in a PCLS model and two models of NAFLD, effectively reduces ammonia and prevents progression of hepatic fibrosis providing a potential novel therapeutic approach for NAFLD.

SAT057

Absence of histidine triad nucleotide binding protein-2 (HINT-2) triggers mitochondrial dysfunction and aggravates steatosis

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Background and Aims: Mitochondrial dysfunction plays a role in the development hepatic steatosis. Histidine triad nucleotide-binding protein 2 (Hint-2) is a mitochondrial adenosine phosphoramidase expressed in hepatocytes. Hint2 knockout mice show hepatic steatosis and lysine hyperacetylation of mitochondrial proteins, which are features of respiratory chain malfunctions. We asked whether the absence of Hint-2 impairs mitochondria bioenergetics secondary to hyperacetylation.

Methods: *Hint2*$^{-/-}$ mice (C57Bl/6J) were generated using homologous recombination. Oxygen consumption rates (OCRs) was measured with the extracellular flux XF-24 bioanalyzer. Acetylation was assessed by immunoprecipitation and immunoblotting.

Results: *Hint2*$^{-/-}$ hepatocytes showed protein hyperacetylation, produced less ATP ($p < 0.001$) and generated a lower mitochondrial membrane potential than did *Hint2*$^{+/+}$ hepatocytes. The basal, ATP-linked and maximal OCRs were decreased in *Hint2*$^{-/-}$ hepatocytes ($p < 0.05$). Palmitate oxidation was reduced by 25% in Hint2$^{-/-}$ mitochondria and triglyceride content was higher in *Hint2*$^{-/-}$ than in *Hint2*$^{+/+}$ hepatocytes ($p < 0.005$). A high fat diet aggravated the hyperacetylation and steatotic phenotype in *Hint2*$^{-/-}$ livers. SNU-449 and HepG2 cells under- or over-expressing Hint-2 did not change protein acetylation. In Hint-2 overexpressing SNU-449 and HepG2 cells, the basal, ATP-linked and maximum OCRs were increased, whereas in Hint-2 silenced HepG2, OCR was decreased. LCMS/MS proteomics identified hyperacetylated proteins active in intermediary and ketone metabolism and in mitochondrial respiration, which were substrates of sirtuin3. Sirtuin3 deacetylase activity *in vitro* was unchanged. The global hyperacetylation status in *Hint2*$^{-/-}$ hepatocytes was partially reversed by recombinant sirtuin3 and NAD^+. Conversely, the acetylation reaction was enhanced *in vitro* in *Hint-2*$^{-/-}$ hepatocytes. An excess of acetyl-CoA (10 mM) increased acetylation 2-fold in *Hint2*$^{-/-}$ hepatocytes relative to *Hint2*$^{+/+}$. In addition, blocking fatty acid oxidation with etomoxir increased acetylation only in *Hint2*$^{-/-}$ hepatocytes.

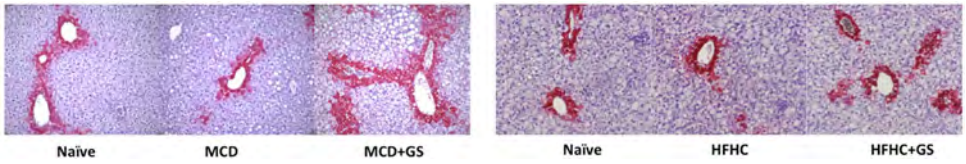

Figure: (abstract: SAT056): Glutamine synthetase (GS) immunohistochemistry (x20) in MCD (A) and HFHC (B) models.

Conclusion: The absence of Hint-2 provokes bioenergetics defects, independent of the global increase in protein acetylation. Our findings support the notion that conditions favoring enhanced acetylation rather than impaired deacetylation are operative in *Hint2*$^{-/-}$ hepatocytes. The bioenergetic deficit in hepatocytes lacking Hint-2 likely leads to the secondary outcome of steatosis.

SAT058

GPNMB modulates hepatic steatogenesis and liver cancer

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Background and Aims: Lipid accumulation in liver cells predispose to non-alcoholic fatty liver disease (NAFLD) including its severe disease types non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC). Hepatocyte (HC)-derived glycoprotein non-metastatic melanoma B (Gpnmb) was recently reported as regulator of fat metabolism in adipose tissue, however, its role in the pathogenesis of NAFLD-related HCC is not clear.
Method: Results: To get insight, we started with an analysis of published microarray data from human patients and found Gpnmb upregulated in NAFLD/NASH and HCC, as compared to healthy livers. We next confirmed a progressively increasing expression of GPNMB in fatty livers (6, 8 and 12 weeks) and HCC stages (20 weeks) of STAM mice, a NASH-based HCC mouse model. With IHC, we locate GPNMB expression to hepatocytes and HC-derived cancer cells. In line, *in vitro* modeling of steatosis by supplementing oleic acid (OA) to mouse hepatocytes (pmHC) and AML-12 cells induces GPNMB expression at mRNA and protein levels. We next modulated GPNMB expression in pmHC and AML12 cells with or without OA-treatment and investigated the fatty hepatocyte phenotype. *Gpnmb* depletion increases triglycerides (TG) accumulation, and mRNA expression of lipogenic genes namely, Sterol regulatory element-binding protein-1c (*Srebp-1c*), Peroxisome proliferator-activated receptor alpha (*Ppar-alpha*), Peroxisome proliferator-activated receptor gamma (*Ppar-gamma*), Fatty acid synthase (Fasn) and stearoyl-CoA desaturase 1 (Scd1). Unexpectedly, Carnitine palmitoyltransferase I (*Cpt1*) and acyl-CoA oxidase 1 (*Acox1*), members of antioxidant genes, are also upregulated. Complementary results were obtained upon GPNMB overexpression. Moreover, in Huh7, HLE and HLF liver cancer cells, GPNMB facilitates cell death signals as measured by time-lapse live cell imaging and caspase assay. Mechanistically, GPNMB facilitates cell death via interfering with AKT phosphorylation dependent survival signals.
Conclusion: GPNMB is a consistently upregulated target in NASH and HCC. GPNMB is expressed in HC and HC-derived cancer cells. In fatty liver, GPNMB is upregulated to tone down lipogenesis. In liver cancer cells, GPNMB acts as a tumor suppressor by providing cytostatic effects. The German Federal Ministry of Education and Research (BMBF) Project LiSyM supported this study.

SAT059

TM6SF2 E167K variant increases the severity of NAFLD in high fat diet-fed mice

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Background and Aims: Genetic factors contribute to the development and progression of non-alcoholic fatty liver disease (NAFLD). Accumulated studies had been conducted to explore the association of Tm6sf2 E167 K with the risk of various liver diseases which includes NAFLD. Although the role of Tm6sf2 E167 K in NAFLD is relative doubtless, the detailed mechanism of Tm6sf2 E167 K in the

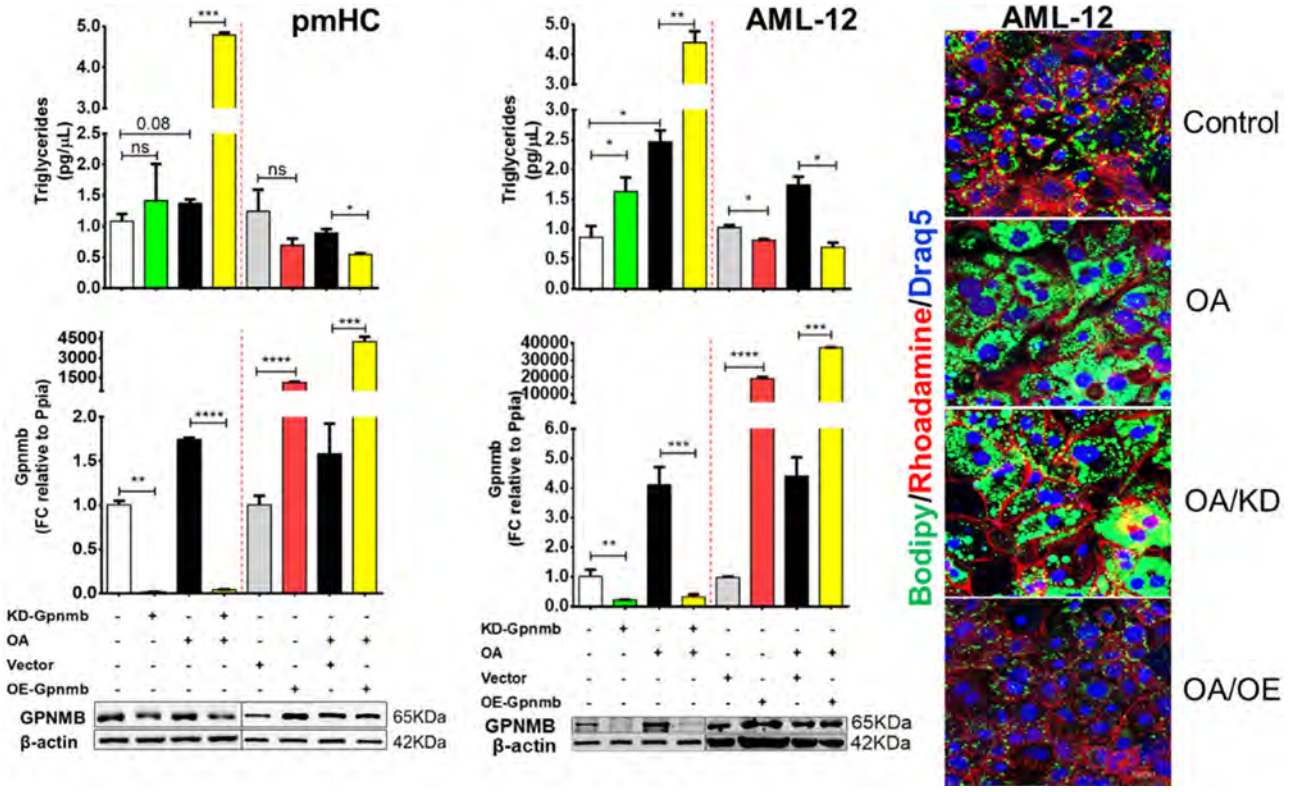
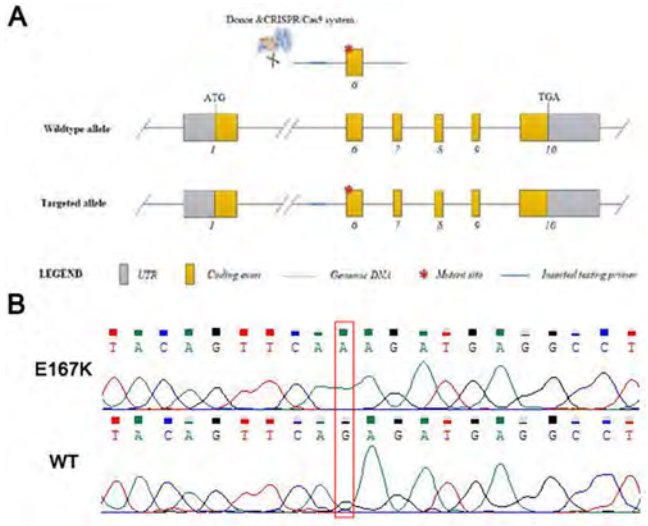


Figure: (abstract: SAT058): Modulation of Gpnmb expression is associated with lipid accumulation in pmHC and AML-12.

development of NAFLD was remains unclear. The aim of this study was to investigate the mechanism of Tm6sf2 E167 K in the development of NAFLD in mouse.

Method: We constructed the Tm6sf2 E167 K mutational C57BL/6 mouse model. The mice were divided into Tm6sf2$^{167E/E}$ group (n = 7) and Tm6sf2$^{167K/K}$ group (n = 7). Mice in each group were fed with chow diet or high fat diet for 8 weeks and 16 weeks. The body weight of each mouse was recorded weekly. Blood and liver of each mouse were sampled, and the liver weights were recorded and the liver indexes were calculated. Hematoxylin-eosin (HE) staining and oil red O staining were conducted to investigate the liver pathological characteristic and lipid accumulation. The HOMA-IR values were calculated to explore the insulin resistance of mice in each group.



Results: Tm6sf2 E167 K mutational C57BL/6 mouse model was constructed successfully. No significant difference of body weights was observed between Tm6sf2$^{167E/E}$ and Tm6sf2$^{167K/K}$ mice when fed with chow diet, but HFD-fed mice were more weight than CD-fed mice, and HFD-fed Tm6sf2$^{167K/K}$ mice were more weight than HDF-fed Tm6sf2$^{167E/E}$ mice. The liver index of Tm6sf2$^{167K/K}$ mice is significant higher than Tm6sf2$^{167E/E}$ mice after fed with HFD for 16 weeks. HE staining and oil red O staining showed that exacerbated hepatosteatosis and more lipid droplets were existed in the HFD-fed Tm6sf2$^{167K/K}$ mice compared to the HDF-fed Tm6sf2$^{167E/E}$ mice. The serum lipid profiles in the HFD-fed Tm6sf2$^{167K/K}$ mice were also significant higher than in the HDF-fed Tm6sf2$^{167E/E}$ mice. Homeostatic model assessment for insulin resistance (HOMA-IR) indexes was augmented by Tm6sf2$^{167K/K}$ variant. CD-fed Tm6sf2$^{167K/K}$ mice developed a more severe form of glucose intolerance than HDF-fed Tm6sf2$^{167E/E}$ mice at 8 weeks and 16 weeks.

Conclusion: Tm6sf2 E167 K variant increases the severity of NAFLD in the mouse after fed with HFD significantly. The detailed mechanism of Tm6sf2 E167 K variant in the development of NAFLD is studying at the present.

SAT060

Unrevealing the HDL lipidome in NAFLD: a possible explanation for the increased CVD risk of these patients

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Background and Aims: Recently, Non-alcoholic Fatty Liver Disease (NAFLD), the most common chronic liver disease, has been appointed as an independent cardiovascular disease (CVD) risk factor. No specific and sensitive biomarker for the diagnosis and progression of the disease has been found as yet. Recent data suggest that the quality of HDLs affect their structure and physicochemical properties, and possibly their ability to protect against atherosclerosis.

The aim of this study was the investigation of the alterations occurring in the HDL lipidome in NAFLD by ^{1}H NMR spectroscopy, in order to identify new biomarkers for the early diagnosis of the disease and to compare it with that recorded from patients with coronary heart disease, in order to elucidate the mechanisms of the increased CVD risk of these patients.

Method: Serum samples were collected from overall 60 cases, out of which 20 patients with NAFLD (diagnosed with abdominal ultrasound), 20 patients with established coronary heart disease and 20 healthy controls. The lipid profile of the HDL lipoproteins was investigated by proton nuclear magnetic resonance (^{1}H NMR) spectroscopy.

Results: Patients with NAFLD exhibited significant changes in HDL lipidome compared to healthy subjects largely attributed to the phospholipid pattern (glycerophospholipids and sphingolipids). Specifically, patients with NAFLD showed reduced % content of phosphatidylcholine and phosphatidylinositol compared to controls and increased sphingolipid content mainly due to increased content of ceramides. The average chain length of fatty acids and the % content of polyunsaturated fatty acids such as arachidonic, eicosapentaenoic and docosahexaenoic acid were found to be reduced in patients with NAFLD compared to the control group. Compared to CVD patients, those with NAFLD showed an increased content of sphingolipids, sphingomyelin, ceramides and reduced content of phosphatidylinositol.

Conclusion: The changes observed in the phospholipid pattern and fatty acids of HDLs in NAFLD patients compared to healthy controls follow the lipid changes observed in hepatocytes of NAFLD patients and possibly reflect the lipid metabolism abnormalities involved in the pathophysiology of NAFLD. Thus, the altered lipidome of HDL may serve as potential biomarker of disease progression. Additionally, these changes seem to affect the atheroprotective properties of HDLs and may partly explain the increased risk of CVD in NAFLD patients.

SAT061

A novel small molecule modulating the mitochondrial NEET (CISD) proteins activity improves inflammation and fibrosis in a diet-induced model of non-alcoholic steatohepatitis

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Background and Aims: Non-alcoholic steatohepatitis (NASH) is a disease characterized by excessive fat accumulation, inflammation and fibrosis in the liver with periportal inflammation having been identified as a marker of disease severity. Here, we present a novel chemistry that regulates the function of 3 mitochondrial proteins called the NEET proteins to target the periportal region of the liver. These proteins perform an important role in mitochondrial Fe/ROS homeostasis and the regulation of mitochondrial metabolism. Previous literature reports have highlighted the therapeutic importance of NEET proteins in metabolic disease, so we assessed the possible effects of ENYO's lead NEET protein modulator on the pathology associated with a diet-induced obesity model of NASH in mice and compared those effects with OCA treatment.

Method: NEET proteins are unique in their ability to reversibly bind two [2Fe-2S] clusters allowing protein function to be evaluated by a

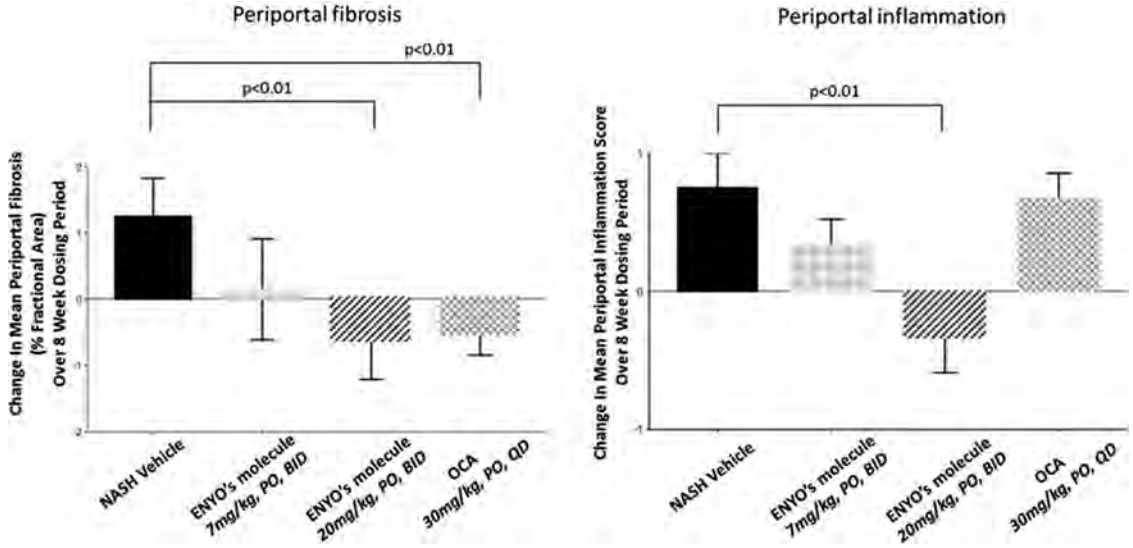

Figure: (abstract: SAT061)

cluster binding assay. Effects on mitochondrial activity were assessed by evaluating (1) mitochondrial respiration by high-resolution respirometry, (2) the activity of electron transport chain complexes by enzymology and finally (3) mitochondrial membrane potential by measuring TMRM probe incorporation by flow cytometry. The effect of ENYO's molecule was investigated *in* vivo by 8 weeks of oral administration in a mouse diet-induced NASH model. For comparison, a mouse group was also administered OCA daily.

Results: ENYO's lead molecule was shown to enhance release of the bound [2Fe-2S] cluster of purified NEET proteins and partially inhibit Electron Transport Chain Complex I and oxidative phosphorylation. Consistent with this effect, mitochondrial membrane potential and mitochondrial ATP levels of treated cells were decreased. In vitro, the molecule showed potential for anti-inflammatory effects by inhibiting NFKB activation in a reporter cell line and IL6 expression in bone marrow-derived macrophages. In vivo, therapeutic administration of ENYO's lead NEET protein modulator was shown to resolve both portal inflammation and portal fibrosis in a dose-dependent manner. Effects seen on portal inflammation were superior to OCA, which showed little effect on portal inflammation.

Conclusion: Our molecule offers a novel approach for regulating the activity of a family of proteins of critical importance in mitochondrial biology and could offer new perspectives in the treatment of NASH and other diseases with an important inflammatory component.

SAT062

Evaluation of pharmacological intervention using a deep learning approach for histopathological scoring in a diet-induced obese and biopsy-confirmed mouse model of NASH with fibrosis

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Background and Aims: The primary endpoint in clinical trials for non-alcoholic steatohepatitis (NASH) is the NAFLD-activity score (NAS) including fibrosis staging in a liver biopsy. Histopathological disease scoring systems are, however, subjective and prone to inter- and intra-observer variation. The present study aimed to develop deep learning applications (APPs) to obtain a more accurate and objective method for staging disease in mouse models of NASH. Further, we evaluated the effect of elafibranor or semaglutide in a diet-induced obese (DIO) biopsy-confirmed mouse model of NASH using the deep learning APPs.

Method: Segmentation of liver biopsy sections stained for H&E and Picro Sirius Red (PSR) from DIO NASH mice and lean controls was performed using the Artificial Intelligence (AI) software from Visiopharm. Hepatocytes with and without steatosis and inflammatory cells were annotated in H&E sections. In PSR sections, portal triads and central veins were segmented using AI. Portal, sinusoidal, and bridging fibrosis were identified using Bayesian image analysis. APP outputs were postprocessed into the corresponding scores (AI scores).

Digital slides were acquired from DIO-NASH mice (C57Bl/6J mice fed AMLN diet) with different stages of steatosis, inflammation and fibrosis (n = 110) to validate the AI scores. Additionally, pharmacological intervention was evaluated on DIO-NASH mice (n = 12–14/group) before (prebiopsy) and after 8 wks treatment with vehicle, elafibranor (30 mg/kg) or semaglutide (30 nmol/kg). AI scores (steatosis, inflammation and fibrosis) were obtained using the deep learning APPs.

Results: The deep learning APPs successfully recognized hepatocytes with and without steatosis, inflammatory cells and portal, sinusoidal and bridging fibrosis in DIO-NASH mice. APP outputs were successfully translated into steatosis, inflammation and fibrosis scores with weighted kappa values of 0.95, 0.81 and 0.74 respectively. Treatment with elafibranor or semaglutide significantly improved steatosis. In addition, animals treated with elafibranor showed no worsening of fibrosis as compared to vehicle. AI scores correlated well with previous reported efficacy data of elafibranor and semaglutide.

Conclusion: We here demonstrate a deep-learning based approach to obtain the NAS and fibrosis scores in a translational DIO-NASH mouse model. A deep-learning approach for pattern recognition allows unbiased and reproducible quantification of histological NASH parameters.

SAT063

MET409, a potent, non-bile acid sustained FXR agonist, improves NAFLD activity score and exerts anti-fibrotic effects in a diet-induced obese mouse model of biopsy-confirmed fibrosing NASH

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Background and Aims: The farnesoid X receptor (FXR) is a ligand activated transcription factor highly expressed in the liver and intestinal tract. Sustained FXR activation has shown efficacy in

clinical trials for non-alcoholic steatohepatitis (NASH); notably in conjunction with anti-fibrotic action. The present study aimed to explore the effect of MET409, a potent non-bile acid sustained FXR agonist, on metabolic, biochemical and histopathological endpoints in a diet-induced obese (DIO) mouse model of biopsy-confirmed NASH with fibrosis.

Method: Male C57BL/6J mice were fed Gubra Amylin NASH (GAN) diet high in fat, fructose and cholesterol for 35 weeks prior to liver pre-biopsy. Only animals with biopsy-confirmed steatosis (≥2) and fibrosis (≥F1) were included and stratified into treatment groups. DIO-NASH mice received vehicle (PO, QD), MET409 (3 mg/kg, PO, QD) or MET409 (10 mg/kg, PO, QD) for 8 weeks. Pre-post liver biopsy histology was performed for within-subject evaluation of changes in NAFLD Activity Score (NAS) and fibrosis stage. Additionally, terminal quantitative liver histology, blood and liver biochemistry was assessed. Finally, whole liver RNAsequencing for transcriptomic profile was analyzed.

Results: MET409 low and high dose treatment induced a weight loss of 14% and 19%, respectively, in DIO-NASH mice. Compared to vehicle, MET409 dose-dependently reduced plasma levels of liver enzymes (ALT, AST) and lipids (triglycerides, cholesterol) after 4 weeks of treatment, being sustained at termination. In addition, MET409 markedly reduced liver triglyceride and cholesterol content. MET409 treatment profoundly reduced quantitative levels (% fractional area) of liver fat and inflammation and improved composite NAS (pre-to-post) for all MET409-treated animals, driven by reduction in steatosis and lobular inflammation scores. For fibrosis, MET409 high dose treatment decreased liver collagen 1a1 content, along with a non-significant improvement in fibrosis stage (pre-to-post). Notable, MET409 treatment reduced liver α-SMA deposition. Finally, MET409 treatment led to consistently lowered expression of hepatic genes associated with inflammation and fibrogenesis.

Conclusion: MET409 is a potent, systemic, sustained FXR agonist that improved metabolic, biochemical and histopathological parameters in biopsy-confirmed DIO-NASH mice. FXR agonists with profiles similar to MET409 are promising drug candidates for improvement in liver pathology by improving fibrosing NASH and preventing fibrogenesis.

SAT064

S1pr2 is a key mediator of endoplasmic reticulum stress in NAFLD/NASH pathogenesis

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Background and Aims: The pathogenesis of non-alcoholic fatty liver disease (NALD), particularly the mechanisms whereby a minority of patients develop a more severe phenotype characterised by hepato-cellular damage, inflammation, and fibrosis is still incompletely understood. Endoplasmic reticulum (ER) stress is a feature of acute and chronic liver diseases through its involvement in inflammatory responses, steatosis, hepatocyte apoptosis, and fibrosis. However, the pathways activated by ER stress driving these processes are still poor unknown. The sphingosine-1-phosphate receptor 2 (S1PR2), one of receptors binding sphingosine-1-phosphate, plays an important role in promoting hepatic regeneration after liver injury and in regulating hepatic lipid metabolism. Nevertheless, its involvement in the NAFLD/NASH pathogenesis remains to be elucidated. Here we investigated the implication of S1PR2 the NAFLD/NASH pathogenesis.

Method: S1PR2 expression was analyzed in liver biopsies from 15 patients affected from NAFLD/NASH at different stages of disease progression and in non-tumoral liver samples from 5 patients with hepatocarcinoma as healthy controls by qRT-PCR. Experimental NAFLD model was carried out in S1PR2−/− (ko) and littermate wildtype (WT) mice by high fat diet (HFD)-feeding for 12 weeks. Body weight, metabolic parameters including total cholesterol, glucose and insulin were recorded. NAFLD activity score (NAS) and steatosis were evaluated by hystology. Inflammatory cytokines were analyzed by ELISA assay. ER stress was induced by a single injection of tunicamycin (TM) at a dose of 1 μg/g body weight intraperitoneally. Unfolded protein response (UPR) signaling was analyzed by qRT-PCR and western blot.

Results: Significant downregulation of S1PR2 was found in NAFLD/NASH patients compared to healthy controls, whereas no difference was observed among the different stages of disease. The genetic deletion of S1PR2 under HFD regime induced greater liver injury, apoptotic and inflammatory signaling, altered metabolic parameters such insulin resistence, reduced glucose level, lower total cholesterol and increased hepatic steatosis associated to a higher NAS score ($p = 0.017$) and to a greater presence of hepatocellular ballooning ($p < 0.001$) compared to WT mice. Significant increase of ATF6, ATF4 and CHOP levels were associated to ko mice compared to WT after HFD and TM treatment, whereas GRP78 levels drastically reduced. Furthermore, the loss of S1PR2 drove to lipid perturbations such as increased uptake of triglyceride and reduction of its oxidation.

Conclusion: These results suggest that S1PR2 is a key mediator of ER stress response, preventing an excessive and/or prolonged UPR activation, which leads to ER stress-induced damage and lipid perturbations. Overall, these observations identify S1PR2 as a novel therapeutic target for the treatment of NAFLD/NASH

SAT065

Infiltrative monocyte derived adenosine deaminase 2 promotes liver fibrosis via signaling through extracellular inosine

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Background and Aims: Liver fibrosis in nonalcoholic fatty liver disease (NAFLD) is driven by infiltrated monocytes. However, the mechanism of this process is not fully understood. We have previously reported an association between liver fibrosis in NAFLD and circulating levels of adenosine deaminase 2 (ADA2), an enzyme produced exclusively by monocytes and macrophages that converts extracellular adenosine to inosine. Herein, we describe a novel mechanism by which infiltrated monocytes secret ADA2 to modulate the phenotype of hepatic macrophages and promote liver fibrosis in NAFLD.

Method: We examined ADA2 expression in 92 liver biopsies from a NAFLD registry. Recombinant human ADA2 was produced to study its function in modulating macrophage's phenotype *in vitro*. Transcriptome analysis in human monocyte-derived macrophages (MoMF) and primary human Kupffer cells were determined in response to wild-type and mutant ADA2 stimulation.
Results: In the human liver, ADA2 expression was noted in CD14+/CD16+ portal macrophages and Kupffer cells. ADA2+ portal macrophages were significantly associated with the degree of liver fibrosis as shown by a quantitative histological score. Notably, portal macrophages carried far more ADA2 transcripts than Kupffer cells as measured by RNAscope, suggesting a putative paracrine and autocrine nature of regulation. Upon ADA2 stimulation, human MoMF demonstrated a striking upregulation of pro-inflammatory and pro-fibrotic genes in our RNAseq analysis. These findings were validated in U937-derived macrophages and human MoMF from six independent donors. Among these differentially expressed genes, PDGF-BB transcription, a key pro-fibrotic cytokine, was upregulated in macrophages in response to ADA2 and its substrate adenosine. Particularly, inosine, the catalytic product of ADA2, stimulated significantly PDGF-BB expression in macrophages, suggesting a causal role of the deaminase activity. Furthermore, mutation at glutamic acid 359 in the catalytic active site of ADA2 resulted in diminished enzyme activity and a reduction in PDGF-BB gene-expression in macrophages compared to native form of ADA2. Finally, we tested the effect of ADA2 in a human-derived multicellular liver spheroid system and found a robust stimulation of PDGF-BB production from primary human Kupffer cells.
Conclusion: Infiltrative monocytes release ADA2 to promote liver fibrosis by augmenting a pro-fibrotic differentiation of hepatic macrophages via signaling through extracellular inosine. This pathway may provide alternative targets in modulating liver fibrosis in NAFLD.

SAT066

TERN-501, a potent and selective agonist of thyroid hormone receptor beta, strongly reduces histological features and biomarkers of non-alcoholic steatohepatitis associated pathology in rodent models

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Background and Aims: Liver inflammation and damage resulting from hepatic fat accumulation are key drivers in the progression of non-alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH). Selective agonists of thyroid hormone receptor beta (THR-beta) have been shown to markedly reduce liver fat, hepatic inflammation, and damage. This drug class may also provide additional clinical benefits to NASH patients by lowering proatherogenic factors.
Method: THR agonist potency and selectivity were assessed biochemically using THR-beta or THR-alpha/RXR heterodimeric assays. Serum cholesterol lowering activity was assessed 24 hours after a single IP dose of TERN-501 in rats fed with a cholesterol rich diet for 14 days. TERN-501 was tested in a mouse NASH model using C57/Bl6J mice fed with a high fat diet prior to biweekly administration of carbon tetrachloride and daily oral drug treatment. Following 28 days of TERN-501 treatment, liver histology was used to assess steatosis, inflammation, ballooning and fibrosis; liver tissue and plasma/serum enzyme, lipid and triglyceride levels were analysed relative to vehicle treated control mice. Gene expression changes were determined by RT-qPCR and RNAseq.
Results: TERN-501 exhibited potent and selective THR-beta agonism (THR-beta EC_{50} = 100 nM; THR-alpha EC_{50} = 2,600 nM) with good PK properties in preclinical species. In a rat hypercholesterolemic model, a robust and dose-dependent reduction in total cholesterol of up to 71% at a dose of 30 mg/kg ($p < 0.0001$ vs. vehicle) was observed. In a NASH mouse model, steatosis in TERN-501 treated mice was profoundly reduced from untreated control mice. Significant reductions in serum total cholesterol, triglyceride and ALT levels were also observed at all dose levels tested. RT-qPCR and RNAseq analysis confirmed modulation of known THR-beta regulated genes. TERN-501 treatment strongly modulated expression of genes in multiple metabolic pathways relevant to NASH.
Conclusion: TERN-501 is a potent and selective THR-beta agonist. TERN-501 reduced serum cholesterol levels in a hypercholesterolemic rat model and significantly reduced liver steatosis, fibrosis, and serum markers of liver damage in a NASH mouse model, supporting further development of this drug for the treatment of NASH.

SAT067

Western diet induced nuclear NFATC1 activates pro-apoptotic endoplasmic reticulum (ER) stress signaling, and progresses NAFLD to NASH

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver diseases worldwide having 20%-30% prevalence. It initiates with hepatocytes lipid

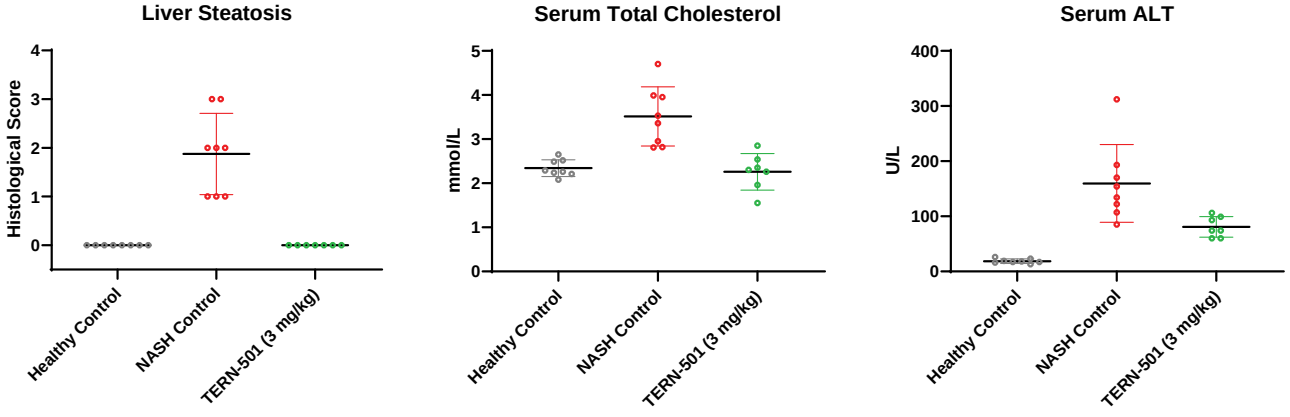

Figure: (abstract: SAT066): TERN-501 significantly reduced liver steatosis and serum total cholesterol and ALT in a mouse model of NASH.

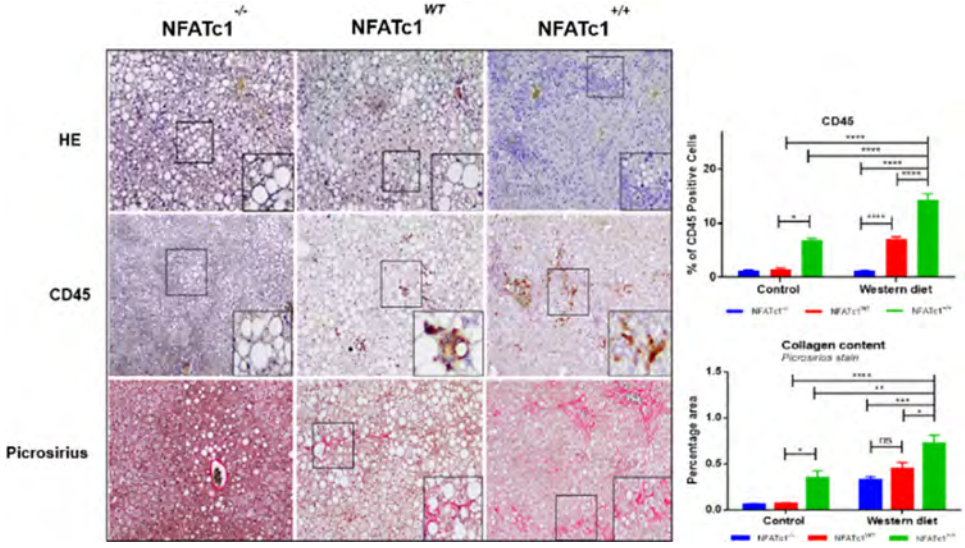

Figure: (abstract: SAT067)

deposition (steatosis) progressing to non-alcoholic steatohepatitis (NASH) and liver cancer. Numerous studies documented aberrant NFAT (nuclear factor of activated T-cells) signalling inducing inflammation and tumor development in other organs e.g. Pancreas. We tend to characterize NFATc1 mediated genes and signalling in NAFLD-NASH-HCC progression.

Method: Immunohistochemistry (IHC) confirmation of NFATc1 activation in NAFLD patients' biopsies. Analysis of palmitate induced NFATc1 expression in mouse primary hepatocytes and AML12 cells by western blot (WB) and immunoflouresence (IF). 8 weeks old C57BL/6 mice with hepatocyte specific constitutively active (NFATc1$^{+/+}$), knock-out and wild type NFATc1 expression (NFATc1^{WT}) were fed with normal and western diet for 20 weeks, respectively. Steatosis, inflammation and fibrosis were analyzed using Hematoxylin-eosin, IHC and picrosirius-red staining. RNA-seq was performed in AML12 cells after transfection with NFATc1$^{+/+}$ construct. Results were validated *in-vivo* and *in-vitro* using RT-PCR and WB. Cytokine profiling was performed in mouse liver tissue lysates.

Results: Western diet/Palmitate activates NFATc1 in hepatocytes both *in-vivo* and *in-vitro*. NFATc1 aberrant expression induced progressive hepatic inflammation and fibrosis in NFATc1^{WT} and NFATc1$^{+/+}$ mouse model. NFATc1$^{-/-}$ mice were protected against western diet induced inflammation and fibrosis. RNA-seq analysis in AML12 cells showed upregulation of pro-inflammatory and pro-apoptotic ER stress signaling after NFATc1$^{+/+}$ transfection, particularly PERK regulated C/EBP homologous protein (CHOP). CHOP leads to activation of caspase-1 mediated apoptosis and induction of pro-inflammatory cytokines IL1-alpha and IL1-beta. NFATc1 silencing protected CHOP induction and apoptosis as analyzed by TUNEL and WB. Mice pretreated with western diet showed similar effects along with NFATc1 dependent changes in cytokines/chemokines. we observed NFATc1 dependent NAFLD progression to NASH. Inhibition of ER stress with tauroursodeoxycholic acid significantly reduced inflammation and fibrosis upon western diet treatment in NFATc1^{WT} and NFATc1$^{+/+}$ mouse.

Conclusion: Together, our ongoing study proposes a model in which NFATc1 induction drives inflammation and fibrosis via inducing hepatocytes ER stress induced apoptosis and pro-inflammatory cytokines.

SAT069

Chorionic-plate-derived mesenchymal stem cells attenuate hepatic steatosis via restoration of mitochondrial function

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Background and Aims: Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases worldwide, but its pathophysiology is not fully understood due to complexity of the mechanisms involved in the disease. Moreover, the pharmacological therapy for NAFLD is not yet available. We investigated the effects of chorionic-plate-derived mesenchymal stem cells (CP-MSCs) on hepatic steatosis and mitochondrial function.
Method: HepG2 cells were treated with palmitic acid (PA), and then co-cultured with CP-MSCs. Intracellular lipid accumulation was measured by oil red O staining and mitochondrial function was assessed by quantifying mitochondrial DNA (mtDNA) and fatty acid oxidation. Male C57BL/6J mice were chronically fed with high-fat diet (HFD). At week 29, mice were injected with either phosphate-buffered saline (NTx) or CP-MSCs (Tx; 1 × 106 cells, 8–10 passages). Four weeks later, liver histology and function were assessed.
Results: PA-induced intracellular lipid accumulation was attenuated when co-cultured with CP-MSCs (panel A). The mitochondrial mass was reduced by PA treatment and then was restored following co-culture with CP-MSCs (panel B). Expression of genes involved in regulation of mitochondrial function, such as PGC1 and sirtuins, was dynamically changed by PA treatment and CP-MSC co-culture. Cellular reactive oxygen species production was increased by PA treatment and then was attenuated after CP-MSC co-culture. The activity of superoxide dismutases (SODs) and the rate of mitochondrial β oxidation were suppressed by PA treatment and were restored by co-culture with CP-MSCs (panel C and D). Severe hepatic steatosis in HFD-fed mice was ameliorated following transplantation of CP-MSCs (panel E). Decreased activity of SODs was reverted to near the levels of normal diet-fed mice after transplantation of CP-MSCs (panel F).
Conclusion: Hepatic steatosis and mitochondrial dysfunction in NAFLD can be ameliorated by transplantation of CP-MSCs. Our study findings suggest the therapeutic potential of CP-MSCs in NAFLD and help understanding alterations in hepatic lipid metabolism which may be restored by CP-MSC transplantation.

SAT071

Iron loss-induced mitophagy via mitochondria ferritin suppresses NASH-related hepatocellular carcinoma

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Background and Aims: Mitochondrial dysfunction is known to play a critical role in nonalcoholic steatohepatitis (NASH) development and subsequent progression to cirrhosis and hepatocellular carcinoma (HCC). Mitochondrial quality is controlled by selective removal of defective mitochondria through autophagy (mitophagy). An iron chelator-mediated iron loss triggers mitophagy by a yet unknown mechanism and whether this could be used to improve mitochondrial function as a therapeutic strategy for NASH has not been tested. The aim of this study was to elucidate whether iron loss-induced mitophagy suppresses the HCC development in NASH-related mouse model and to clarify the mechanisms by which iron loss induces mitophagy.
Method: The effect of iron chelator, deferiprone (DFP), on mitophagy was examined using Huh7 cells, HepG2 cells, and NASH-related hepatocarcinogenic mouse models (STAM mice and 7,12-dimethylbenz(*a*)anthracene (DMBA)-treated mice fed a high fat diet).
Results: Iron loss induced by DFP suppressed NASH-related liver fibrosis and HCC development by inducing mitophagy in the mouse liver. Among the mitochondria-associated iron regulatory proteins, DFP treatment resulted in increased expression of mitochondrial ferritin (FTMT). In human liver cells, a transcription factor, SP1 and its regulator hypoxia inducible factor 1 alpha were necessary for DFP-induced increase in FTMT expression. FTMT is the mitochondrial protein that is synthesized as a precursor on cytosolic ribosomes, targeted to mitochondria, and then processed into functional protein.

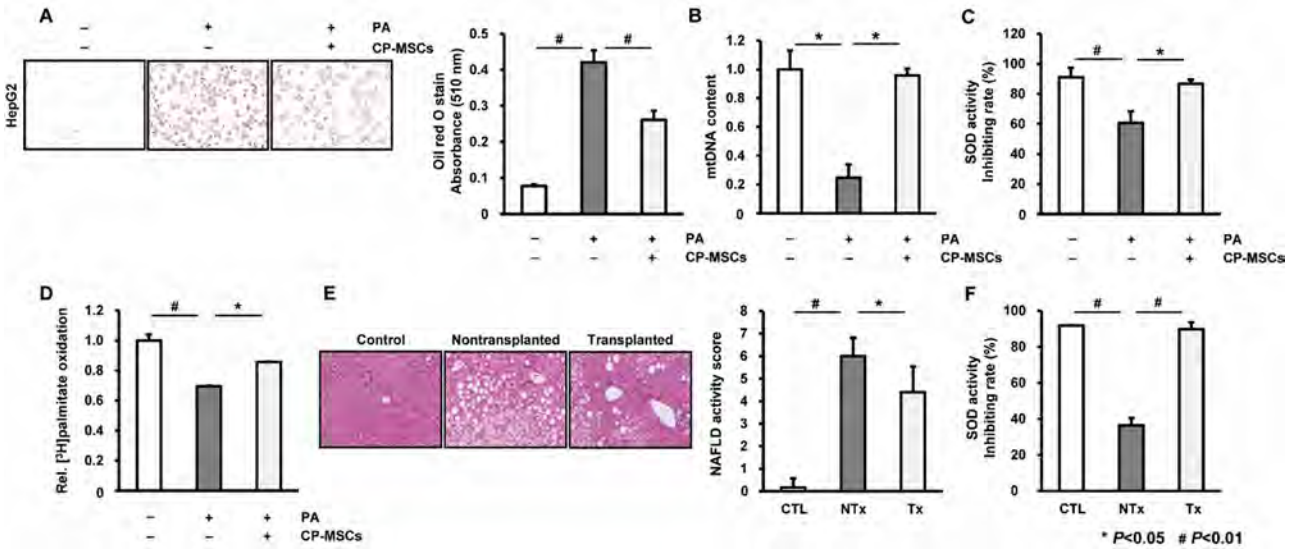

Figure: (abstract: SAT069)

DFP treatment accumulated FTMT on the outer membrane of defective mitochondria. FTMT specifically interacted with nuclear receptor coactivator 4, autophagic cargo receptor. Silencing FTMT abolished DFP-induced mitophagy. The hepatic iron decrease itself did not suppress HCC development since FTMT knockdown abrogated DFP-induced suppression of HCC. The expression of FTMT positively correlated with the number of mitophagosome-like structures and negatively correlated with the pathological severity and progression of nonalcoholic fatty liver disease (NAFLD) in liver biopsy specimens obtained from patients with NAFLD.
Conclusion: These results provide a rationale for targeting mitophagic activation as a therapeutic strategy against NASH-related liver fibrosis and HCC development.

Cirrhosis and its complications: Clinical

SAT076
Application of the new GLIM criteria for the diagnosis of malnutrition in patients with liver cirrhosis and usefulness of three different screening tools

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Background and Aims: Different scientific societies have proposed GLIM criteria (Global Leadership Initiative on Malnutrition) for the diagnosis of malnutrition. In patients with liver cirrhosis, however, the prevalence of such malnutrition has not been evaluated by applying these criteria. Our principal aim was to analyze the prevalence of malnutrition in a cohort of patients with liver cirrhosis according to the new GLIM criteria. As a secondary objective, to evaluate the capacity of the Liver Disease Universal Screening Tool (LDUST), Royal Free Hospital-Nutrition Priorizing Tool (RFH-NPT) and Mini Nutritional Assessment Short Form (MNA-SF) questionnaires as screening tools for malnutrition.
Method: Prospective study including consecutively all patients with liver cirrhosis in follow-up in Hepatology consultations at the Miguel Servet Universitary Hospital during the months of April and May 2019. Initially, a gastroenterologist applied the screening tools: LDUST, RFH-NPT and MNA-SF. Subsequently, the diagnosis of malnutrition was carried out according to GLIM criteria by an endocrinologist blind to the results of the screening tools. Sarcopenia was evaluated by bioimpedanciometry.
Results: 63 patients (38.1% women, mean age 63.11 ± 9.92) with cirrhosis (60.3% Child-A, 34.9% Child-B and 4.8% Child-C) were evaluated. The most frequent causes were alcohol (53%) and hepatitis C (23.8%). The prevalence of malnutrition according to GLIM criteria was 38.1% (15.9% moderate, 22.2% severe). The prevalence of sarcopenia was 14.3%. The most prevalent GLIM criteria were reduction in strength measured by hand grip (27%) and reduction in dietary intake (36.5%). Advanced stages of cirrhosis were associated with higher prevalence of malnutrition ($p = 0.033$). Considering GLIM as the gold standard, MNA-SF was the most accurate screening tool, being superior to RFH-NPT and LDUST (Table 1). It presented better sensibility than NFH-NPT (67% [0.45;0.84] vs 87% [0.67:0.97], $p = 0.031$) and better specificity than LDUST (97% [0.86; 0.99] vs 62% [0.44;0.76], $p < 0.001$) and than NFH-NPT (97% [0.86; 0.99] vs 82% [0.66;0.92], $p = 0.016$).

Table: Screening tools statistical measures

	LDUST	RFH-NPT	MNA-SF
Sensitivity % (IC)	83% (0.62;0.95)	67% (0.45;0.84)	87% (0.67:0.97)
Specificity % (IC)	62% (0.44;0.76)	82% (0.66;0.92)	97% (0.86; 0.99)
PPV % (IC)	57% (0.46;0.67)	80% (0.69; 0.88)	92% (0.81;0.97)
NPV % (IC)	85% (0.70;0.94)	70% (0.52;0.82)	95% (0.75;0.99)
Positive likelihood ratio	2,10 (1.40;3.34)	3.71 (1.79;7.69)	34.125 (4.90;237.60)
Negative likelihood ratio	0,27 (0.11;0.69)	0,41 (0.23;0.73)	0,1 (0.04;0.37)

Conclusion: According to the GLIM criteria, the prevalence of malnutrition in patients with cirrhosis is very high, being severe in 22% of the patients. The MNA-SF is the most accurate screening test, superior even to tools specifically designed for patients with cirrhosis.

SAT077
Automated low flow ascites (ALFA) pump effectively reduces the number of large volume paracentesis - data from a real world cohort

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Background and Aims: The alfapump is an implantable device which removes fluid from the peritoneal cavity into the urinary bladder and which is therefore used as a therapy for cirrhosis related refractory ascites and malignant ascites. The aim of our study was to analyze the safety and efficacy of the alfapump in a real life cohort.
Method: In this retrospective study we included all patients (n = 35) who underwent the alfapump implantation in the University Hospital Leipzig between June 2013 and September 2019. The major criteria to consider alfapump in our clinic are contraindication for TIPS and life expectancy of 6 months and more. The number of large volume paracenteses (LVP), clinical data and technical device reports were collected from patient records before and 1 week (±3 days) 3, 6, 12, 18, 24 months (±1 month) after implantation.
Results: Patients who underwent the procedure had a mean age of 62.3 ± 8.8 years and 77.1% were male. The main cause of ascites was liver cirrhosis (n = 32, 91.4%) and of those the majority had an alcoholic liver disease (n = 25, 78%). There were three patients with ascites unrelated to cirrhosis, caused by HCC in non-cirrhosis, mastocytosis and pancreas carcinoma (n = 1 each). At the time of implantation the median glomerular filtration rate (GFR) was 55 mL/min (20–112), mean MELD in cirrhotic patients was 13.4 ± 3.6. The median time the pump was functioning was 205 (29–933) days and the mean ascites volume removed was 740 ± 386 mL per patient/day. The LVP frequency per month could be reduced from 3.0 ± 1.1 to 0.8 ± 1.4 ($p = 0.001$). During the follow up wound complications such as dehiscence, cellulitis and local infection occurred in 11 (31.4%), technical issues such as catheter occlusion/kink and device defects in 9 (25.7%) patients. Overall 14/35 did not reach the targeted 6 months follow up (5 died due to progression of the liver disease, 7 pumps were explanted and 2 were implanted less than 6 months ago). Creatinine increased in 17/35 patients during the first week (mean 37.2 ± 38.7 µmol/L) and was significantly enhanced in patients with pre-existing renal insufficiency (GFR < 89 mL/min), 43.1 vs 14.8 µmol/L, $p = 0.01$. 4/7 patients (57.1%) fulfilling the AKI-criteria responded to

therapy. Overall 10 patients (28.5%) developed a spontaneous bacterial peritonitis (SBP), without difference between those, who had a history of SBP and those who developed SBP de novo (3/9 vs. 7/26, p = 0.6). Infections (local or systemic) led to pump removal in 12 (34.2%) patients, after a median time of 184 (46–555) days. Other reasons for explantation were ascites resolution (n = 3) and device defect (n = 3).

Conclusion: The alfapump significantly reduces the LVP-frequency and therefore is a relevant therapeutic option for patients with difficult to treat ascites. The management of renal function especially in patients with preexistent insufficiency and infection surveillance are crucial in the follow up period.

SAT078

Covered TIPSS does not improve long term survival in refractory ascites - a single- centre experience

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Background and Aims: Refractory ascites is a serious complication of cirrhosis and portal hypertension with a 1 year survival rate of 50%. In selected patient treatment options include liver transplantation or TIPSS (transjugular intrahepatic portosystemic shunt). A recent trial showed better outcomes with covered TIPSS(1). The aim of this project was to assess the outcomes of patients who underwent a TIPSS compared to those who had large volume paracentesis (LVP).

Method: We performed a retrospective study of all patients who underwent a covered TIPSS for refractory ascites from April 2010 to November 2017 compared to all patients who underwent LVP (mean 1.28 ± 0.55 paracenteses per month) during a similar time period. We compared biochemical and clinical parameters. The primary outcome was transplant free survival.

Results: The ratio of patients in each group was 1:1.1 (n = 76 in TIPSS group, n = 86 in LVP group).

There was a male predominance of 53% and 60% respectively in the TIPSS and LVP group. The mean ages were 59 ± 9.5 & 61 ± 11.4 years. The most prevalent aetiology was alcohol related liver disease (75% TIPSS group; 56% LVP group).

The MELD score was significantly higher in the LVP group (11.5 ± 3.8 vs 15.6 ± 5.2, p < 0.05). 10 patients in the TIPSS group underwent liver transplantation versus 26 patients in the LVP group. There was no difference in spontaneous bacterial peritonitis presence between groups. Overall follow up was 20 ± 20.6 months.

Transplant free survival time at 6,12,24,60 months is as follow: TIPSS: 76%, 64%, 50%, 21%; LVP group 79%, 55%, 38%, 19% (p = NS, Figure 1). No clinical or biochemical variables were associated with survival on cox regressions analysis.

The TIPSS group (n = 76) was compared with a subset of patients in the LVP group (n = 48) who would be considered suitable for TIPSS based on the following parameters (platelet count ≥ 75 10^9/L, bilirubin ≤ 50 micromol/L, absence of pre-exist hepatic encephalopathy(2)). A further analysis of these groups showed transplant free survival remained similar in both groups.

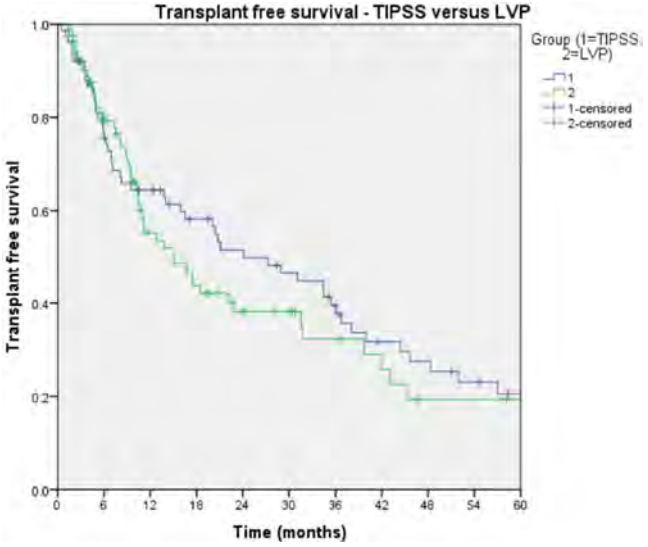

Figure: Transplant free survival (KP curve).

Conclusion: Our study shows that covered TIPSS did not result in improved transplant free survival when compared to LVP in a real-world cohort of patients with advanced liver failure. We can conclude that liver transplantation remains the best option for refractory ascites in selected patients. Further controlled studies to identify prognostic markers to assist clinicians in selecting appropriate candidates for TIPSS are required.

References

1. Bureau C, Thabut D, Oberti F, Dharancy S, Carbonell N, Bouvier A, et al. Transjugular Intrahepatic Portosystemic Shunts With Covered Stents Increase Transplant-Free Survival of Patients With Cirrhosis and Recurrent Ascites. *Gastroenterology*. 2017;152(1):157–63.
2. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol*. 2018;69(2):406–60.

SAT079

Comparison of skeletal muscle index (SMI) and transversal psoas muscle thickness (TPMT) for the diagnosis of sarcopenia in cirrhosis

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Background and Aims: Sarcopenia is a condition of progressive and generalized loss of muscle mass, strength and physical performance. Although physiologic in aging, sarcopenia represents an important burden in patients with liver cirrhosis due to its correlation with negative out-comes. Skeletal Muscle Index (SMI) is considered the gold standard for the diagnosis of sarcopenia and is calculated with computed tomography (CT) and specific due to these reasons, researchers have proposed different techniques, faster and easier, as the Trasversal Psoas Muscle Thickness (TPMT). The aim of this study is to analyze the differences among these two effective detecting sarcopenia tools.

Method: The abdominal CT of each patient has been studied to find both SMI and TPMT. SMI were taken at L3 level and the sarcopenia cut-off are: SMI ≤ 3 8.5 cm^2/m^2 for women and SMI ≤ 5 2.4 cm^2/m^2 for men. TPMT has been calculated at the level of the umbilicus and the sarcopenia cut-off are: TMPT ≤ 1 4 mm/m for women and TMPT ≤ 1 7.8 mm/m for men. Images have been studied with SliceOmatic V4.2 software, to find the total value of area.

Results: One-hundred eighty-one patients were included. A linear correlation showed these two tools are well correlated (r = 0,63 con p < 0,001), even considering only the male population (r = 0,62, p < 0,001) or the female one (r = 0,58, p < 0,001). Using SMI, we found 81 cases of sarcopenia, instead using TPMT 65 cases. The TPMT could not find out 22 cases of sarcopenia, and considered 6 patients more than SMI as affected by disease. Therefore, TMPT underestimates 27% of patients in the diagnosis, showing a sensibility of 73% and specificity of 94%.
We found both sarcopenia-SMI and sarcopenia-TPMT were significantly associated with mortality.
Conclusion: Due to lower sensitivity TPMT should not replace SMI for the diagnosis of sarcopenia in cirrhotic patients.

SAT080

PPIs can be discontinued in over 60% of patients with cirrhosis: long term impact of screening for hepatitis C drug interactions

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Background and Aims: Proton pump inhibitors (PPIs) are commonly prescribed in patients with cirrhosis. However, use of these drugs in this cohort has been associated with increased risk of spontaneous bacterial peritonitis and development of hepatic encephalopathy. Indications for long term use of PPIs in cirrhosis should be regularly reviewed and treatment discontinued wherever possible. PPIs can result in reduced absorption of some direct acting antivirals (DAAs) resulting in potentially sub-therapeutic levels which may impact on DAA efficacy. Frequently, it may be advised to reduce the dose or stop the PPI for the duration of HCV therapy to minimise the impact of this interaction.
We aimed to investigate whether temporary discontinuation or dose reduction of PPI therapy during HCV treatment as a result of a drug-drug interaction would result in long term rationalisation of the PPI prescription.
Method: Patients with cirrhosis commencing HCV treatment between April 2017 and March 2019, in Glasgow treatment centres were identified from the local HCV database. Information on co-prescription of PPIs was taken from pharmacy records and electronic patient records checked to confirm current prescribing status of PPI. Baseline data on age, gender, CP score, DAA regimens, PPI regimen and doses was collected. Management of the DDI was categorised as: PPI stopped and stayed off, PPI stopped and restarted after treatment, PPI dose reduced and remained low, PPI dose reduced and increased after treatment or no change to PPI.
Results: Seventy-three patients (70% male, mean age 52.3 (±SD) years) with cirrhosis co-prescribed PPIs were identified. Ten patients had decompensated liver disease (3 CPB, 7 CPC). Thirty-one patients (42.5%) were prescribed a combination of DAA and PPI which did not require discontinuation or adjustment of the PPI. Of 33 patients who stopped PPI therapy due to HCV treatment, 21 (63.6%) remained off PPIs once treatment completed. Nine patients had their dose of PPI reduced secondary to a potential DDI, with 5 (55.5%) staying on the reduced dose post treatment.
Conclusion: The majority of patients who stopped a PPI due to concerns of DDI with HCV DAAs were able to remain off the PPI once HCV treatment was completed. DDI assessment provides a valuable opportunity to rationalise medications that are potentially harmful in the context of advanced chronic liver disease, and provide an important benchmark for the feasibility of doing so.

SAT081

Building a better mousetrap: can MELD-Na be improved?

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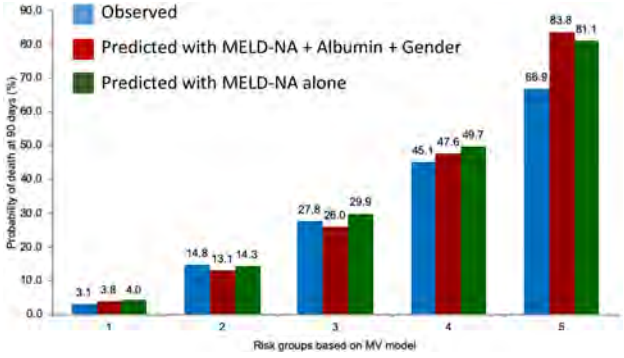
Building a better mousetrap: Can MELD-NA be improved?

Background and Aims: MELD-NA is a well-established prognostic indicator for short term mortality in patients with end-stage liver disease (ESLD). It has been suggested that the predictive accuracy of MELD-NA has decreased recently with changing demographics of liver disease. The aim of the study is to utilize modern data in patients with ESLD and determine whether incorporation of additional variables may improve the accuracy of MELD-NA.
Method: This analysis is based on data from the US national registry of liver transplant candidates listed between Jan 2016 and Dec 2018. Patients were divided into model development (70%) and validation (30%) data sets. We develop a mortality prediction model using a multivariable Cox proportional hazards regression analysis incorporating additional prognostic variables. The impact of each variable on mortality was carefully modeled through variable transformation, thresholds, and interactions. Model discrimination was evaluated by concordance (c) statistics, and calibration was evaluated by comparing expected and observed mortality rates.
Results: The registry included 21,059 eligible liver transplant candidates with ESLD, divided into 14,742 for the development set and 6,317 for the validation set. After screening all potential predictors of mortality, two variables, namely sex and serum albumin, were found to be predictive of 90-day mortality, in addition to the four existing variables in MELD-NA. Statistically significant interaction was found between bilirubin and sodium, bilirubin and albumin, and sodium and INR. In the final optimized model, despite the addition of new variables and interactions, the c-statistic for the development cohort was not higher than MELD-NA alone (0.845 versus 0.846). In the validation data set, the new score predicted 90-day mortality quite well across all risk strata. However, the figure shows that the model's mortality prediction was not superior to MELD-NA. The c-statistics of the two models in the validation set were also comparable (both 0.857).



Conclusion: In contemporary ESLD patients awaiting liver transplantation, serum albumin and sex were statistically significant variables predictive of 90-day mortality independent of MELD-NA. However, incorporating these additional variables did not materially improve mortality prediction by MELD-NA. MELD-NA remains a robust and practical tool with which to predict short term mortality in patients with ESLD.

SAT082

Systemic inflammation is associated with cardiodynamic state in acute-on-chronic liver failure

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Background and Aims: Acute-on-chronic liver failure (ACLF) is characterized by high short-term mortality and systemic inflammation (SI). Recently, different cardiodynamic states were shown to independently predict outcomes in cirrhosis. The relationship between cardiodynamic states, SI, and portal hypertension and their impact on ACLF development remain unclear. The aim of the present study was therefore to evaluate the interplay of cardiodynamic state and SI on fatal ACLF development in liver cirrhosis.
Method: At inclusion, haemodynamic measures including cardiac index (CI) and hepatic venous pressure gradient (HVPG) of 208 patients were measured. Patients were followed prospectively for fatal ACLF development (primary endpoint). SI was assessed by proinflammatory markers such as interleukins (ILs) 6 and 8 and IL-33 receptor - soluble ST2.
Results: Patients were divided according to CI (<3.2; 3.2–4.2; >4.2 L/min/m^2) in hypo- (n = 84), normo- (n = 69) and hyperdynamic group (n = 55). After a median follow up of 3 years, the highest risk of fatal ACLF was seen in hyperdynamic (35%) and hypodynamic patients (25%) compared to normodynamic (14%) (p = 0.011). Hyperdynamic patients showed the highest rate of SI. The detectable level of IL-6 was an independent predictor of fatal ACLF development.
Conclusion: Cirrhotic patients with hyperdynamic and hypodynamic circulation, have a higher risk of fatal ACLF. Therefore, the cardiodynamic state is strongly associated with SI, which is an independent predictor of development of fatal ACLF.

SAT083

Preliminary results of the effects of beta-hydroxy-beta-methylbutyrate supplementation in patients with liver cirrhosis: a randomized controlled pilot study

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Background and Aims: Frailty is defined as a syndrome of physiological decline in late life. In patients with cirrhosis, the dysregulation of both catabolic and anabolic muscular pathways cause an increased risk of anticipated sarcopenia and frailty. Our goal is to evaluate the effects of a 3 g/die β-hydroxy-β-methylbutyrate (HMB) supplementation for twelve weeks (T1) on muscular mass and performance status in patients with cirrhosis.
Method: Clinical history and blood parameters were collected for each patient at the beginning of the study (T0). Furthermore, not only cognitive (Mini Mental State Examination, Psychometric Hepatic Encephalopathy Score, Animal Naming Test) and physical tests (Six Minute Walking Test, Five Chair Stand, Hand Grip Test) but also anthropometric measurements (using "Quadriceps femoris ultrasound" and Bioimpedentiometry) and Liver Frailty Index (LFI) was performed. Patients were randomized into a treatment group (3 g/die HMB supplementation for 12 weeks) and a control group (3 g/die sorbitol supplementation for 12 weeks). Both groups received nutritional counseling and indications of physical activity to carry out during the treatment period. At the end of the 12 weeks (T1) all the tests and measurements performed at T0 were repeated and the resulting data compared in each patient.
Results: 23 cirrhotic patients have been enrolled at present, 14 of the HMB Group and 9 of the Placebo Group. Patients receiving HMB showed a statistically significant improvement in muscular performance at FCS ranging from 14.5 (±5.4 DS) sec to 11.6 (±2.7 DS) sec, at 6MWT rising from 346.8 (±66 DS) m to 416 (±57 DS) m and LFI, decreasing from 4.0 (±0.4 DS) to 3.7 (±0.4 DS) with p value = 0,008. No significant variation between T0 and T1 were reported in patients assigned to the control group.
Conclusion: The preliminary results of this controlled randomized study suggest the efficacy of HMB supplementation in enhancing muscular performance and subsequently reducing frailty in cirrhotic patients.

SAT084

Optimizing nutrition in patients with cirrhosis may reduce hospital readmissions in medium and high risk groups: a quality improvement project

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Background and Aims: Malnutrition adversely affects prognosis in cirrhosis and is often recognized late. All cirrhotic patients should be screened for malnutrition yet this is variably performed. We evaluated assessment and management of nutrition in cirrhosis by comparing local practice to EASL guidelines, and explored patient outcomes after a focused intervention.
Method: Data was collected in 2 cycles. Cycle 1 retrospectively reviewed nutritional assessment of all patients admitted to gastroenterology during September-December 2018 with cirrhosis. An Inpatient Nutrition Proforma (INP) was introduced to record Child-Pugh (CP), anthropometrics, dietary intake, risk of malnutrition, and nutrition plan. Sarcopenia was assessed in high risk patients using handgrip strength (HGS). All CP-C and BMI <18.5 were high risk. Cycle 2 prospectively audited admissions after intervention (March-June 2019). Calorie-protein intake and HGS after intervention, readmissions and deaths were assessed at 4 months.
Results: 47 and 31 patients were identified in cycle 1 and 2 respectively. A Malnutrition Universal Screening Tool (MUST) was completed in 81% of cycle 1 patients. 47% did not trigger a dietetic referral on MUST scoring (44% medium risk and 33% high risk for malnutrition). All cycle 2 patients had a dietetic referral via the INP (26% medium risk and 71% high risk for malnutrition) and received dietary education with 77% requiring additional oral supplements and 10% nasogastric feeding. At follow-up, cycle 2 patients met higher caloric and protein requirements (average increase by 46% and 57% respectively versus 26% and 31% in cycle 1). HGS was measured in 74% in cycle 2 and 2% in cycle 1. Average HGS was 15.9 kg (cycle 2) and

improved by 9% on reassessment. There was a 12% reduction in hospital readmissions in cycle 2 compared to 7% increase in cycle 1 with similar mortality at 4 months.
Conclusion: MUST scores may be inadequate to identify all cirrhotic patients at risk of malnutrition. CP and BMI appear more accurate. A dedicated dietetic team and the INP enable early patient identification, thorough nutritional assessment and personalized plans, improving patient compliance and sarcopenia. Hospital readmission rates reduced over 4 months despite a higher proportion of high risk patients in cycle 2 versus cycle 1. 12 month follow-up data will be collected to assess mortality more accurately. Our intervention forms a platform for wider service development in this area that will help sustain quality improvement both in the inpatient setting and beyond.

SAT085

Adipopenia, among the nutritional parameters, is the rapid screening tool that best correlates with mortality in decompensated cirrhotic patients: results of a prospective study

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Background and Aims: patients with liver cirrhosis (LC) often have malnutrition (MN) which is associated with decompensation, infection and death. Nevertheless, nutritional status (NS) is rarely evaluated in clinical practice and there is no general agreement on definition and methods, especially in decompensated cirrhosis. Aims of this study were: 1) to investigate the prevalence of MN; 2) its impact on mortality in patients with LC and ascites and 3) relationship between MN and infectious ascites (SBP).
Method: NS was analysed in all cirrhotic patients with ascites consecutively admitted in two clinical Liver Centres between November 2014 and October 2016. The end of study was September 2019. The evaluation of NS was made using anthropometric parameters (weight, height, mid arm circumference, triceps skinfold thickness) and their derivate measurements: BMI according to Campillo, Upper Muscle Area (UMA), Upper Fat Area (UFA). All patients underwent diagnostic paracentesis and were followed up till the end of study to assess the outcome. An independent Ethical Committee approved the study.
Results: 110 patients were included and underwent NS assessment in addition to routine clinical procedures. They were: male 69.1%, median age 61 (range 26–85); aetiology of cirrhosis was: HCV 52.7%, Alcohol 33.6%, HBV 33.6%, Other 12.7%; Child-Turcotte-Pugh Class A 10.9%, B 64.5%, C 24.5%; MELD <14: 43.6%, 14–20: 33.6%, >20: 22.7%; SBP 27.3%. Prevalence of MN was: 30.9% according to corrected BMI, 67.3% according to UMA, and 40% according to UFA. During follow-up (median 10 months), 4 patients (3.6%) underwent OLT and were considered as death. Nineteen patients (17.3%) were lost to follow-up. The percentage of patients alive were: 68.1% at 3 months, 59.3% at 6 months, 45.1% at 12 months, 24.2% at the end of the study. At univariate analysis SBP, MELD, UFA, UMA and age were significantly associated with mortality. At multivariable analysis only SBP, MELD higher than 20, MELD higher than 14 and UFA were independently associated with mortality (OR = 3.09, 2.89, 2.35 and 2.22, respectively). There was a strong correlation between adipopenia and SBP ($p = 0.008$); but not with sarcopenia.
Conclusion: UFA, that measures the adipopenia, was abnormal in 40% of the cirrhotic population investigated and, among the parameters of malnutrition, was the only test independently associated with mortality (odds ratio 2.2).

SAT086

Leptin as a key player in insulin resistance of liver cirrhosis

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Background and Aims: Insulin resistance is associated with increased risk of death and liver transplantation in the cirrhotic population independently of disease aetiology. However, factors accounting for insulin resistance in the context of cirrhosis are incompletely understood. This study aimed to investigate the association between adiponectin and leptin with insulin resistance in cirrhotic patients and to assess the influence of disease severity on insulin resistance and metabolic status.
Method: This cross-sectional study included 126 non-diabetic cirrhotic patients eligible for liver transplantation, who were classified according to Child-Pugh score. Homeostasis Model Assessment 2 model was used to determine insulin resistance index, and adiponectin, leptin, insulin, c-peptide, glucose, HbA1c, and lipid profile were analysed at fasting. We performed stepwise logistic regression to determine predictors of insulin resistance.
Results: Insulin resistance was detected in 83% of the subjects, and associated with higher levels of leptin, fasting plasma glucose and body mass index, and lower levels of triglycerides. Logistic regression analysis identified leptin and triglycerides as independent predictors of insulin resistance (OR 1.247, 95% CI 1.076–1.447, $p = 0.003$; OR 0.357, 95% CI 0.137–0.917, $p = 0.032$.). Leptin levels remained unchanged, whereas adiponectin levels progressively increased ($p < 0.001$) with disease progression, and inversely correlated with HbA1c ($\rho = -0.349$, $p < 0.001$).
Conclusion: Our results indicate that leptin resistance, as indicated by elevated leptin levels, can be regarded as an important contributing factor of insulin resistance in cirrhotic patients. The protective effect of triglycerides against insulin resistance was observed, while progressively increasing adiponectin levels elicited positive effect on glucose homeostasis, but not insulin sensitivity across liver cirrhosis stages.

SAT087

Femur fractures are associated with high morbimortality in patients with cirrhosis

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Background and Aims: Patients with cirrhosis have an increased risk of falls and fractures. Fractures, especially femoral, and related surgical procedures are a common cause of decompensation and mortality in these patients. However, data evaluating the clinical impact of femur fractures in patients with cirrhosis are very scarce. The aim of this study is to evaluate the morbidity and mortality of patients with cirrhosis and femur fractures.
Method: Observational retrospective study including all patients with cirrhosis admitted for femur fracture to our hospital between 2007 and 2019. Patients were identified by the encoded diagnostics of the medical documentation department. Demographic data, clinical features, liver function, type of fracture, treatment, complications and in-hospital mortality were analyzed.

Results: One hundred and two patients were identified, 14 of whom were excluded because of lack of appropriate data, and 88 patients were thus analyzed (age 75.6 ± 11.0, 52.2% women). The main etiology was hepatitis C virus (48.9%), 43.2% had decompensated cirrhosis and MELD at admission was 11.8 ± 4.7. Fractures were the consequence of falls in 96.5% of patients, 97.7% were in proximal femur and 86.3% were operated. The time from admission to surgery was 5.3 ± 4.3 days. The incidence of complications during hospitalization was 56.8%, with infections (44.3%), renal insufficiency (35.2%), ascites (21.6%) and encephalopathy (20.4%) being the most frequent. In-hospital mortality was 18.2% (16/88), mainly due to infections. Mortality was significantly lower in patients who were operated on than in those who were not (13.1% vs 50% p = 0.007). In the multivariate analysis, independent predictive factors of in-hospital mortality were MELD (OR 1.146, 95% CI 1.018–1.290, p = 0.02) and the non-performance of surgery (OR 7.316, 95% CI 1.838–29.117, p = 0.005). Mortality among the five patients with MELD > 21 (all of them operated) was 80%. Neither age nor time between admission and surgery were predictive factors of mortality.
Conclusion: Patients with cirrhosis and femur fractures have a high risk of decompensation and in-hospital mortality. MELD score and the non-performance of surgery were independent predictive factors of mortality. Prevention of falls and multidisciplinary management of patients with fractures, including early assessment by hepatology units, may contribute to improve the prognosis of patients with cirrhosis.

SAT088

The presence of infection during hospitalization is associated with an increased risk of procedure-related bleeding in cirrhosis

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Background and Aims: Patients with decompensated cirrhosis frequently undergo procedures while hospitalized. Bleeding risk related to procedures is understudied and administration of empiric bleeding prophylaxis is common, yet lacks substantial evidence. We examined a cohort of hospitalized patients with decompensated cirrhosis who underwent non-surgical procedures to identify factors predictive of bleeding.
Method: Medical records of 707 hospitalized patients with cirrhosis over 2 years were examined. Patients were excluded if they had surgery, did not undergo a procedure or had non-procedure related bleeding. Bleeding was defined according to established criteria and was related to the procedure in time and location.
Results: 180 patients met inclusion criteria (40 with bleeding group (BG) and 140 in the non-bleeding group (NBG). General characteristics were similar between groups including MELD 26 (95%CI 22–25) BG vs. 23 (95%CI 22–25) NBG, p = 0.13. Traditional measures of coagulation were similar between groups including platelets 111 k/mL (95%CI 87–134) BG vs. 118 k/mL (95%CI 106–131) NBG, p = 0.50, fibrinogen 149 mg/dL (95%CI 118–178) BG vs.167 mg/dL (95%CI 147–189) NBG, p = 0.32, and INR 2.0 (95%CI 1.6–2.4) BG vs. 1.8 (95%CI 1.6–1.9) NBG, p = 0.25. Patients in the BG underwent significantly more procedures (3.6, [95%CI, 2.7–4.4]) than the NBG (2.1 [95%CI, 1.8–2.4]), p < 0.0001). The presence of infection at time of procedure was highly associated with bleeding on univariate analysis (OR 3.0, 95%CI 1.4–6.2, p = 0.0003). On multivariate analysis, infection (OR 2.4, 95% CI 1.1–5.3, p < 0.003), number of procedures performed (OR 1.3, 95% CI 1.1–1.5, p < 0.0001) and total admissions during the study period (OR 1.2, 95% CI 1.1–1.4, p = 0.0026) were independently associated with bleeding. Paracentesis was the most common procedure performed (Table 1). Among patients with bleeding, major bleeding was associated with a significantly larger decrease in hemoglobin and increased transfusion requirements compared to patients with minor bleeding.

Table: Bleeding Events

	Major Bleed (n = 26)	Minor Bleed (n = 14)
Bedside procedure 1. Paracentesis (21) 2. Thoracentesis (2) 3. Lumbar puncture (1)	16 (15.1%)	8 (7.5%)
Vascular (4)	3 (15.7%)	1 (5.3%)
Endoscopic (5)	4 (14.8%)	1 (3.7%)
Interventional radiology (4)	2 (15.4%)	2 (15.4%)
Other (3)	1 (6.7%)	2 (13.2%)

Conclusion: Infection is highly associated with risk of bleeding related to procedures. There is a higher risk of bleeding in patients with active infections who may benefit from personalized pre-procedure prophylaxis or special considerations. Multiple hospitalizations and more frequent procedures were also predictive of bleeding indicating that risk increases with a longer and more complicated hospital course. Future prospective studies are needed to create a predictive model in this population that will aid in accurate risk assessment.

SAT089

Role of urinary neutrophil gelatinase-associated lipocalin, kidney injury molecule-1 and cystatin C as markers of mild kidney function impairment in patients with liver cirrhosis

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Background and Aims: Renal function impairment worsens prognosis in patients with liver cirrhosis. Early diagnosis of chronic kidney disease poses a challenge for clinicians.
The aim of the study was to establish possible usefulness of urinary neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1) and cystatin C (CysC) as early markers of mild impairment of kidney function in patients with liver cirrhosis.
Method: Urine samples from 95 consecutive patients with liver cirrhosis of different etiologies were collected within 24 hours after admission to the 1st Department of Infectious Diseases Regional Specialistic Hospital, Wroclaw, Poland. Urinary concentrations of NGAL, KIM-1, CysC and proteinuria were mesured. eGFR according to Modification of Diet in Renal Disease equation was calculated and Child-Turcotte-Pugh score (CTP) was performed.
ANOVA and t-Student tests were used. P value 0.05 was considered statistically significant.
Results: According to CTP score 57 patients were in A group, 32 patients - B and 6 patients - C. Mean eGFR was 92.2 ml/min/1.73m^2 and did not differ significantly between CTP A, B and C groups (95.3, 87.4 and 88.2 respectively). Mean NGAL, KIM-1 and CysC concentrations between the group with higher eGFR (≥90 ml/min/1.73 m^2, N = 51) and lower eGFR (<90 ml/min/1.73 m^2, N = 44) did not differ significantly (NGAL: 33.87 pg/mL vs 32.32 pg/mL, KIM-1: 1.88 ng/mL vs 1.59 ng/mL, CysC: 27.77 ng/mL vs 22.4 ng/mL respectively). Patients with proteinuria (N = 30) had significantly higher urinary concentrations of NGAL (50.23 pg/mL) than patients without proteinuria (N = 65, mean NGAL = 24,82 pg/mL), p = 0.0056. KIM-1 and CysC were not statistically different in these groups (KIM-1: 2.67 ng/mL vs 1.35 ng/mL, CysC 36.2 ng/mL vs 19.7 ng/mL respectively). However in patietns with proteinuria there were no statistically

significant differences in NGAL concentrations between the subgroup with higher eGFR (≥90 ml/min/1.73 m^2, N = 19, NGAL = 53.57 pg/mL) and lower eGFR (<90 ml/min/1.73 m^2, N = 11, NGAL = 43,92 pg/mL).

Conclusion:

9. Urinary NGAL, KIM-1 and CysC possibly will not play a role as early makers of mild impairment of renal function in patients with liver cirrhosis.
10. Urinary NGAL, but not KIM-1 or CysC reflects proteinuria in patients with liver cirrhosis.
11. Urinary NGAL does not reflect renal function in patients with proteinuria and liver cirrhosis.

SAT090

Analysis of factors associated with the prognosis of cirrhotic patients who were treated with V2-receptor antagonist for hepatic edema

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Background and Aims: V2-receptor antagonist named tolvaptan has not yet been added to the EASL guidelines. In Japan, a phase 3 clinical trial demonstrated the efficacy and safety of tolvaptan for cirrhotic patients with hepatic edema. Accordingly, in 2013, the use of tolvaptan for patients complicated by hepatic edema was approved. Contrary to the EASL guidelines, tolvaptan can be administered to patients resistant to treatment with conventional diuretics in Japan. We conducted a retrospective, multi-center collaborative study to identify the prognostic factors and clarify whether on-treatment factors, including conventional diuretic dosages and short-term response to tolvaptan, affect the long-term prognoses in cirrhotic patients with hepatic edema.

Method: Patients were initially instructed to receive salt-restricted diet therapy and conventional diuretics. When the BW of the patients remained unchanged on treatment, tolvaptan was orally administered at a dosage of 7.5 mg/day. Short-term responders to tolvaptan were defined as patients with BW loss of ≥1.5 kg from baseline to day 7.

Results: Patients consisted of 266 males and 141 females, with the median age of 68 years. The frequency of short-term responders to tolvaptan was 59.7%. In the Cox regression analysis, short-term response to tolvaptan, average dosages of furosemide and spironolactone during tolvaptan, Child-Pugh classification, and presence of hepatocellular carcinoma were independent factors associated with 1-year survival. The 1-year and long-term cumulative survival rates in short-term responders were significantly higher than those in non-responders (P = 0.011 and 0.010, respectively). Using a receiver operating characteristic curve analysis, the optimal cut-off values of average daily dosages of furosemide and spironolactone for predicting 1-year survival were 19 mg/day and 23 mg/day, respectively. The long-term cumulative survival rates in patients who received a mean dosage of spironolactone <23 mg/day during tolvaptan treatment period were significantly higher than those receiving a mean dosage of ≥23 mg/day (P = 0.001).

Conclusion: This study suggests that the short-term response to tolvaptan and low dosages of conventional diuretics during tolvaptan treatment improve the 1-year and long-term survival rates in cirrhotic patients with hepatic edema, irrespective of liver and kidney function and the presence of hepatocellular carcinoma.

SAT091

Combination of meld and lactates predicts early death in patients treated by salvage tips for refractory variceal bleeding

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Background and Aims: Few data are available about the short-term prognosis of salvage TIPS using covered stents for refractory variceal bleeding in cirrhotic patients in Baveno consensus IV/V/VI. The aims of this study were to assess survival and identify risk factors of early death in these patients.

Method: We retrospectively studied 164 cirrhotic patients from 5 centers, treated with salvage TIPS for refractory variceal bleeding between 2007–2017 divided in a derivation cohort (83 patients, 3 centers) and a validation cohort (81 patients, 2 centers). The association between clinico-biological variables the day of the TIPS, and 6-week mortality was assessed using uni and multivariable Cox models. A score including MELD and lactates was developed in the derivation cohort and evaluated in the validation cohort.

Results: Among the 83 patients of the derivation cohort, 78% were male with a median age of 55 years, 76% had alcoholic cirrhosis, 79.5% with esophageal varices, median MELD was 19 and median arterial lactates level 3.7 mmol/L. 77% of patients received vasopressors, 87% oral tracheal intubation and 17% renal replacement therapies. 11% of patients experienced acute pulmonary edema, 14.5% variceal rebleeding and 41% encephalopathy within the 6 weeks after TIPS.
The 6-week mortality was 42% (90% for MELD ≥3 0, 76% for lactates ≥ 5 mmol/L and 100% for lactates > 12 mmol/l). In multivariate analysis, the MELD score (OR = 1.1, 95%CI[1.06–1.14], p < 0.001) and lactates (OR = 1.1, 95%CI[1.08–1.17], p < 0.001) were independently associated with 6-week mortality. In the derivation cohort, we created a score combining MELD and lactates and a value > 3,53 was associated with 100% 6-week mortality (p < 0.001, AUROC 0.84).
The characteristics of the 81 patients of the validation cohort were not different compared to those of the derivation cohort (median MELD 18, median lactates 2,42 mmol/L). The 6-week mortality was 33% (87% for MELD > 30, 53% for lactates ≥ 5 mmol/L and 100% for lactates > 12 mmol/l). The 6-week mortality with a MELD-lactates score >3,53 was 87% and had higher predictive performances (AUROC = 0.70) than MELD (AUROC = 0.60) and lactates alone (AUROC = 0.66).

Conclusion: After salvage TIPS for refractory acute variceal bleeding, 6-week mortality remains high and can be predicted by a combination of MELD and lactates. This score can help to select a subgroup of patients with a better prognosis and use all resources available to prompt salvage TIPS in those patients.

SAT092

Esophageal varices recurrence after eradication: are there any predictors ?

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Background and Aims: Esophageal varices (EVs) are a life-threatening complication of portal hypertension. Endoscopic variceal ligation (EVL) is the main instrumental treatment either on primary or secondary prophylaxis. But after varices eradication remains the risk of variceal recurrence (VR) and consequently the risk of bleeding. The aim of our study was to evaluate the recurrence rate of EVs and to determine the predictive factors of VR.
Method: We performed a single-center retrospective study analyzing data of patients with cirrhotic portal hypertension undergoing EVL for primary or secondary prophylaxis during 2010 to 2017. Patients aged under 17 years were excluded. Platelet count to spleen diameter ratio (PSR), AST-to-ALT ratio, APRI, FIB-4, Kings'score, Lok index, cirrhosis discriminant score, Goteborg University Cirrhosis Index (GUCI), MELD score were calculated for each patients at the first EVL. EVs recurrence was defined as an increase in EVs size to ≥ grade 1 after first eradication. Biochemical, endoscopic and imaging data was collected.
Results: Overall eighty-nine patients were included with a sex ratio M/F = 1.02. The mean age was 55.9 years ± 14.17. Child-Pugh class distribution was A (37%), B (51%), C (12%). A total of 267 EVL sessions were performed with an average number of banding sessions per patients of 3 sessions (1–7). Median follow-up was 53.5 months (mean: 68.7 months). Eradication was obtained in 89% of cases. Varices recurred in 41% of patients with a mean period of 28.9 ± 17.37 months after eradication. In univariate analysis secondary prophylaxis (OR 9.6; 95% CI 1.146–80.394; p = 0.017), portal thrombosis (OR 3.7; 95% CI 1,228–11,533; p = 0.03), *peri-esophageal collateral veins* (OR 9.7; 95% CI 2.486–38.021; p = 0.003), portal hypertensive gastropathy (OR 2.9; 95% CI 1.075–8.001; p = 0.03), APRI (p = 0.008), Fib-4 (p = 0.014), Lok index (p = 0.009), GUCI (p = 0.017) and PSR (p < 0.00001) were significantly associated with VR. In multivariate regression analysis only PSR (OR 0.99; 95% CI 0.996–0.999; p = 0.002) was an independent factor associated with VR. The area under the curve (AUC) of PSR as predictor of VR was 0.786 (95% CI 0.676–0.897; p < 0,00001). The optimal cutoff value of PSD predicting VR was 513 (sensibility 74%, specificity 75%).
Conclusion: PSR may be a reliable noninvasive predictor for recurrence of oesophageal varices. Thus we propose a cutoff of 513 to identify patients at high risk of variceal recurrence in order to optimize screening after eradication. PSR is a promising tool, requiring more studies in order to be integrated into a new risk score of variceal recurrence.

SAT093

Sarcopenia is associated with lack of therapeutic response and higher mortality in hepatocellular carcinoma patients

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Background and Aims: Hepatocellular carcinoma (HCC) is a dreadful complication of liver cirrhosis.
Aim: To study the effect of sarcopenia on treatment response, morbidities, and survival in patients with HCC.
Method: Two hundreds and sixty-two patients with HCC were included and subjected to different therapeutic modalities according to BCLC classification. Patients were followed for 12 months. Basal sarcopenia and follow up values were calculated by skeletal muscle index (SMI) through examination of psoas muscle at L3 by CT.
Results: patients with sarcopenia (43.1%) were older (61.18 ± 8.32: p = 0.006), mainly males (69.5%; p = 0.042), Child-Pugh class B (55.7%: p = 0.001). Patients with sarcopenia had lower survival than those without (10.09 vs. 11.72 months) p = 0.001. On pairwise comparison of patients with and without sarcopenia in the different time points between the baseline and 1, 3, 6 and 12 months; there was a statistically significant difference (p = 0.001) with higher values (cm^2/m^2) in patients without baseline sarcopenia (52.78 ± 8.32 vs. 44.12 ± 5.34), (51.80 ± 8.41 vs. 43.85 ± 5.77), (50.34 ± 8.12 vs. 43.9 ± 5.45), (49.54 ± 8.28 vs. 43.52 ± 5.31) and (49.28 ± 8.29 vs. 45.72 ± 13.23). On follow up patients with sarcopenia had higher incidence of ascites, compared to those without (45% vs. 20.4%), spontaneous bacterial peritonitis (21.7% vs. 11.6%), upper gastrointestinal bleeding (22.9% vs. 12.7%) and hepatic encephalopathy (28% vs. 11.5%) (p = 0.001). Patients with baseline sarcopenia compared to those without, had higher percentage of progressive HCC despite intervention in the first (29.2 vs. 16.1; p = 0.023), third (40.7 vs. 29.5; p = 0.001), sixth (51.4 vs. 30.6; p = 0.001) and the 12th months (32.1 vs. 25.7; p = 0.001). Recurrence rates at 1, 3,6, 12 months were (69%, 64.6%, 59.2% and 41.8%) for patients with sarcopenia and 57%,47.6%,40.9% and 31.3% for patients without sarcopenia, respectively (p = 0.001). Totally patients with sarcopenia compared to those without had higher (p = 0.001) percentage of progressive HCC (39% vs. 25.5%).

Table comparison of patients with and without sarcopenia			P	
None			Sarcopenia	
149			113	
M ±SD		M ±SD		Total
Age	58.43 ±7.73	61.18 ±8.32	59.61 ±8.09	0.006
BMI	25.17 ±2.40	23.20 ±2.06	24.32 ±2.46	0.001
BCLC	BCLC A 56 (37.6%)	18 (15.9%)	74 (28.2%)	0.001
BCLC B	79 (53.0%)	63 (55.8%)	142 (54.2%)	
BCLC C	14 (9.4%)	32 (28.3%)	46 (17.6%)	
Sarcopenia.3	None 104 (72.2%)	5 (4.4%)	109 (42.4%)	0.001
Sarcopenia	40 (27.8%)	108 (95.6%)	148 (57.6%)	
Sarcopenia.6	None 112 (76.2%)	2 (1.8%)	114 (44.2%)	0.001
Sarcopenia	35 (23.8%)	109 (98.2%)	144 (55.8%)	
Sarcopenia.12	None 106 (76.8%)	11 (20.0%)	117 (60.6%)	0.001
Sarcopenia	32 (23.2%)	44 (80.0%)	76 (39.4%)	
Etiology	Viral negative 3 (2.0%)	3 (2.7%)	6 (2.3%)	0.909
HBV	9 (6.0%)	8 (7.1%)	17 (6.5%)	
HCV	133 (89.3%)	100 (88.5%)	233 (88.9%)	
NASH	3 (2.0%)	2 (1.8%)	5 (1.9%)	
Others	1 (.7%)	0 (0.0%)	1 (.4%)	
Sex	Female 53 (35.6%)	27 (23.9%)	80 (30.5%)	0.042
Male	96 (64.4%)	86 (76.1%)	182 (69.5%)	
Morbidity.S	None 80 (53.7%)	63 (55.8%)	143 (54.6%)	0.887
DM	45 (30.2%)	31 (27.4%)	76 (29.0%)	
HTN	24 (16.1%)	19 (16.8%)	43 (16.4%)	
Smoking	Nonsmoker 123 (82.6%)	77 (68.1%)	200 (76.3%)	0.024
Smoker	11 (7.4%)	14 (12.4%)	25 (9.5%)	
Exsmoker	15 (10.1%)	22 (19.5%)	37 (14.1%)	
Performance.St	PS 0 105 (70.5%)	52 (46.0%)	157 (59.9%)	0.001
PS 1	34 (22.8%)	42 (37.2%)	76 (29.0%)	
PS 2	10 (6.7%)	19 (16.8%)	29 (11.1%)	
Survival.St	Alive/censored 134 (89.9%)	55 (48.7%)	189 (72.1%)	0.001
Dead	15 (10.1%)	58 (51.3%)	73 (27.9%)	
CTP.0	CTP A 96 (64.4%)	50 (44.2%)	146 (55.7%)	0.001
CTP B	53 (35.6%)	63 (55.8%)	116 (44.3%)	
PVT.Mets	None 135 (90.6%)	81 (71.7%)	216 (82.4%)	0.001

Table 7 comparison of different stages of BCLC P

BCLC		A	B	C	Total	
		M ±SD	M ±SD	M ±SD		
		74	142	46		
Age		56.32 ±7.55	60.82 ±8.04	61.20 ±7.70		0.001
BMI		25.62 ±2.56	23.92 ±2.27	23.48 ±2.08		0.001
Sarcopenia.0	None	56 (75.7%)	79 (55.6%)	14 (30.4%)	149 (56.9%)	0.001
Sarcopenia		18 (24.3%)	63 (44.4%)	32 (69.6%)	113 (43.1%)	
Sarcopenia.1	None	53 (71.6%)	74 (52.1%)	7 (15.2%)	134 (51.1%)	0.001
Sarcopenia		21 (28.4%)	68 (47.9%)	39 (84.8%)	128 (48.9%)	
Sarcopenia.3	None	55 (74.3%)	54 (38.0%)	0 (0.0%)	109 (42.4%)	0.001
Sarcopenia		19 (25.7%)	88 (62.0%)	41 (100.0%)	148 (57.6%)	
Sarcopenia.6	None	54 (73.0%)	60 (43.2%)	0 (0.0%)	114 (44.2%)	0.001
Sarcopenia		20 (27.0%)	79 (56.8%)	45 (100.0%)	144 (55.8%)	
Sarcopenia.12	None	52 (74.3%)	65 (58.6%)	0 (0.0%)	117 (60.6%)	0.001
Sarcopenia		18 (25.7%)	46 (41.4%)	12 (100.0%)	76 (39.4%)	
Etiology	Viral negative	2 (2.7%)	2 (1.4%)	2 (4.3%)	6 (2.3%)	0.457
HBV		3 (4.1%)	10 (7.0%)	4 (8.7%)	17 (6.5%)	
HCV		69 (93.2%)	124 (87.3%)	40 (87.0%)	233 (88.9%)	
NASH		0 (0.0%)	5 (3.5%)	0 (0.0%)	5 (1.9%)	
Others		0 (0.0%)	1 (.7%)	0 (0.0%)	1 (.4%)	
Sex	Female	28 (37.8%)	43 (30.3%)	9 (19.6%)	80	0.10

Conclusion: Sarcopenia is associated with lack of response to therapy, liver decompensation and higher mortality in hepatocellular carcinoma patients.

SAT094

A telephone survey to screen for frailty pre-liver transplant evaluation: validation of an easy to use survey

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Background and Aims: Frailty is now an accepted predictor of mortality in the cirrhotic patient. Multiple screening modalities exist to determine patients who currently are frail, or are at future risk of developing frailty; however, they rely on an in-person assessment of the patient. Busy transplant centers currently have no reliable means to measure frailty prior to an initial visit with a provider. The aim of this study is to test the validity a telephone survey of frailty in pre-liver transplantation patients as compared to gold-standard in person assessments.
Method: Patients referred for consideration of liver transplantation at the University of Rochester Medical Center were screened for frailty using a telephone survey between March 2017 and October 2019. The telephone survey was adapted from a previously described telephone-based survey called the FRAIL scale. All patients then underwent frailty testing during their initial office visit using the gold-standard Fried Index. Results of the telephone survey and in-person assessment were then compared.
Results: A total of 79 patients were screened for frailty using the telephone survey prior to their initial in-person assessment. Of those 79 patients 33 (41.7%) were determined to be frail by the telephone survey, and 26 of those patients were found to be frail by the Fried Index for a positive predictive value of 78.8%. While 46 patients (58.3%) were determined to not be frail by the telephone survey, and 30 of those patients were found to not be frail by the Fried Index for a negative predictive value of 65.2%. The sensitivity and specificity of the telephone survey was 61.9% and 81.8% respectively.

	Frail by Fried Index	Not Frail by Fried Index	TOTAL
Frail By Phone Survey	26	7	33
Not Frail By Phone Survey	16	30	46
TOTAL	42	37	

Conclusion: This preliminary investigation indicates that a telephone survey is a useful tool to screen for frailty in pre-liver transplant patients. While not intended to replace gold-standard in person assessments, our telephone survey can be used a simple screen to easily find patients that may benefit from intensive nutrition and physical therapy interventions. Future refinements of this survey will allow for more accurate screening, and potentially improved outcomes for frail patients owing to the speed at which they can be identified.

SAT095

Risk factors associated with mortality in upper gastrointestinal bleeding in cirrhotic patients

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Background and Aims: Comparison of prognostic factors of bleeding in cirrhotic patients according to the etiology of bleeding.
Method: We performed a retrospective study on 647 cirrhotic patients with upper gastrointestinal bleeding, 352 men (54.4%) and 295 women (45.5%), with a mean age 54.56 ± 26.16 years. We divided the cohort into two groups, variceal bleeding (VB) and non-variceal bleeding (NVB), in order to find the prognostic factors for mortality using linear regression and logistic regression.
Results: From 647 patients, 200 (30.9%) had NVB and 447 (69.1%) had VB. The mortality rate was 17.2% in group with VB vs 10% in group with NVB, ($p < 0.0001$). We evaluated three predicting factors for mortality: liver failure defined as Child Pugh B and Child Pugh C class, severity of bleeding defined as severe anemia (Hb < 6 g/dl) and active upper GI bleeding (Table 1).
Conclusion: Liver failure in patients with all sources of bleeding is an independent risk factor for mortality in cirrhotics. Severe anemia turned out to be an independent risk factor for mortality in variceal hemorrhage, but not in patients with non-variceal bleeding. Active bleeding increases the mortality risk only in variceal hemorrhage, but it is not an independent factor.

Table: (abstract: SAT095) Univariate and multivariate analysis

	Overall N = 647		Variceal Bleeding N = 447		Non-variceal Bleeding N = 200	
Parameter	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
Liver failure	P < 0.001	P = 0.01	P < 0.0001	P = 0.003	P < 0.0001	P < 0.01
Severity of bleeding	P = 0.02	P = 0.002	P < 0.0001	P = 0.01	P = 0.23	P = 0.84
Active upper GI bleeding	P = 0.03	P = 0.31	P = 0.04	P = 0.75	P = 0.41	P = 0.89

SAT096

Epithelial cell death markers M65 and M30 are significantly up-regulated in decompensated liver cirrhosis and decreased by correction of portal hypertension

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Background and Aims: In end-stage liver disease, epithelial cell death markers M30/M65 have been suggested as predictors for outcome. While the M30 ELISA detects caspase-cleaved keratin 18 as a marker for epithelial apoptosis, M65 detects keratin 18 (K18) as a global epithelial cell death marker. Both have been suggested as indicators of hepatocyte injury. This study evaluates the hypothesis that an elevated transhepatic pressure gradient promotes hepatocellular injury which can be reverted when portal hypertension is corrected by transjugular intrahepatic portosystemic shunt (TIPS) insertion.
Method: 42 cirrhotic patients with ascitic decompensation who received a TIPS and 9 patients with compensated cirrhosis were included in our prospective cohort study. Peripheral blood was collected before, 4–9 weeks (early follow-up) and 4–10 months (late follow-up) after TIPS insertion and in patients with compensated cirrhosis. Plasma levels of caspase-cleaved K18 were quantified using the M30 Apoptosense ELISA as an indicator for apoptosis. The M65 ELISA (Peviva) which measures total and caspase-cleaved K18 was used to assess the amount of epithelial cell death in plasma. Statistical analyses were performed by using Mann-Whitney test and t test, where applicable.
Results: Both, M30 and M65 were significantly higher in patients with ascitic decompensation compared to patients with compensated liver cirrhosis (p = 0,0034 and 0,0175, respectively). At late follow-up after TIPS insertion, M65 and M30 were both significantly decreased in patients with successful ascites control, indicating sufficient correction of portal hypertension. M65 plasma levels were lowered to the level of the compensated cirrhosis group.
Conclusion: Plasma markers of epithelial cell death are correlated with ascitic decompensation in liver cirrhosis. Therapeutic correction of portal hypertension by TIPS decreases M65 and M30 levels, suggesting a reduction of hepatocellular injury.

SAT097

Bidimensional shear wave elastography of the rectus femoris muscle in patients with cirrhosis

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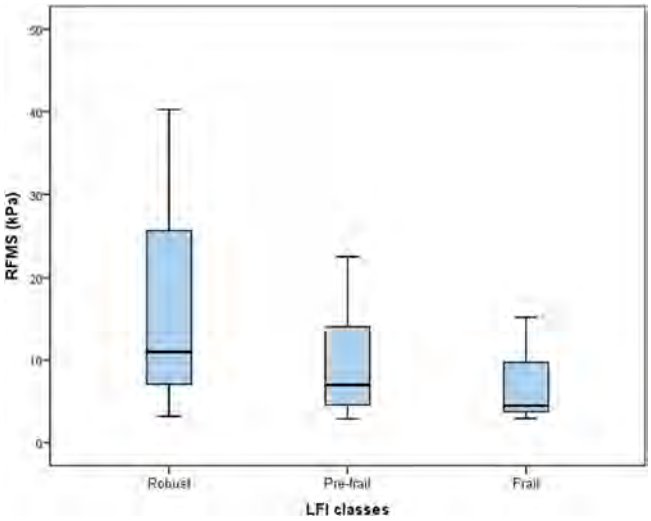
Background and Aims: frailty is a frequent complication of cirrhosis, often related to skeletal muscle abnormalities, increasing mortality. Bidimensional shear wave elastography (2D-SWE) could offer new insights into biomechanical properties of skeletal muscle related to muscle quality. However, no research to date investigated the feasibility and reproducibility of 2D-SWE to assess skeletal muscle stiffness and its relationship with the severity of liver disease and global frailty.
Method: fasting outpatients with cirrhosis undergoing abdominal ultrasound were prospectively included in a single-center. Exclusion criteria were: transjugular intrahepatic portosystemic shunt, >75 years old, known peripheral artery disease, myopathy unrelated to liver disease. Liver Frailty Index (LFI) was used to test global frailty. Skeletal muscle stiffness was studied at the quadriceps femoris by using 2D-SWE (Aixplorer, Supersonic Imagine, France). Three sets of measurements of the rectus femoris muscle stiffness (RFMS) were performed.
Results: 39 patients (21 males; mean age 57 ± 10 years, 24 with alcoholic etiology) have been included. 19 patients were in the Child-Pugh Class A, 16 in class B and 4 in class C. 7 patients were compensated (no previous decompensation), and 32 decompensated. According to LFI classes 3 patients were robust, 28 pre-frail and 8 frail. Compensated and decompensated patients did not show significant differences in LFI classes. RFMS measurement was feasible in all patients, and the three measurements showed a high reproducibility (intraclass correlation coefficient: 0.96; 95% CI 0.93–0.98, p < 0.0001). Median RFMS was 6.4 kPa (IQR 10), with values ranging from 2.9 to 40.3 kPa. No correlation with Child and MELD score was observed. However, RFMS was higher in decompensated vs. compensated patients, in median: 7.4 (IQR 12) vs. 4.5 (IQR 3.3) kPa (p = 0.07), and differed among the LFI classes showing the lowest value in frail patients (11.0 vs. 7.0 vs. 4.5; p = 0.08; Figure).



Conclusion: RFMS measurement on 2D-SWE is feasible and reproducible in patients with cirrhosis and seems independent of liver function. RFMS is higher in decompensated patients, but lower in frail patients vs. pre-frail and robust. This finding, and the observed high variability within each of the LFI classes, suggest that RFMS could be further studied as a potential simple, quantitative non-invasive test to stratify muscle quality in patients with cirrhosis.

SAT098

Bacterial translocation-induced inflammation promotes liver fibrogenesis in patients with advanced chronic liver disease

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Background and Aims: The enhanced liver fibrosis (ELF) score comprises serum markers of matrix remodeling that might also reflect the dynamic process of liver fibrogenesis. A broad body of experimental evidence suggests that bacterial translocation-induced inflammation promotes liver disease progression, however, studies in humans are limited. Accordingly, we investigated whether markers of

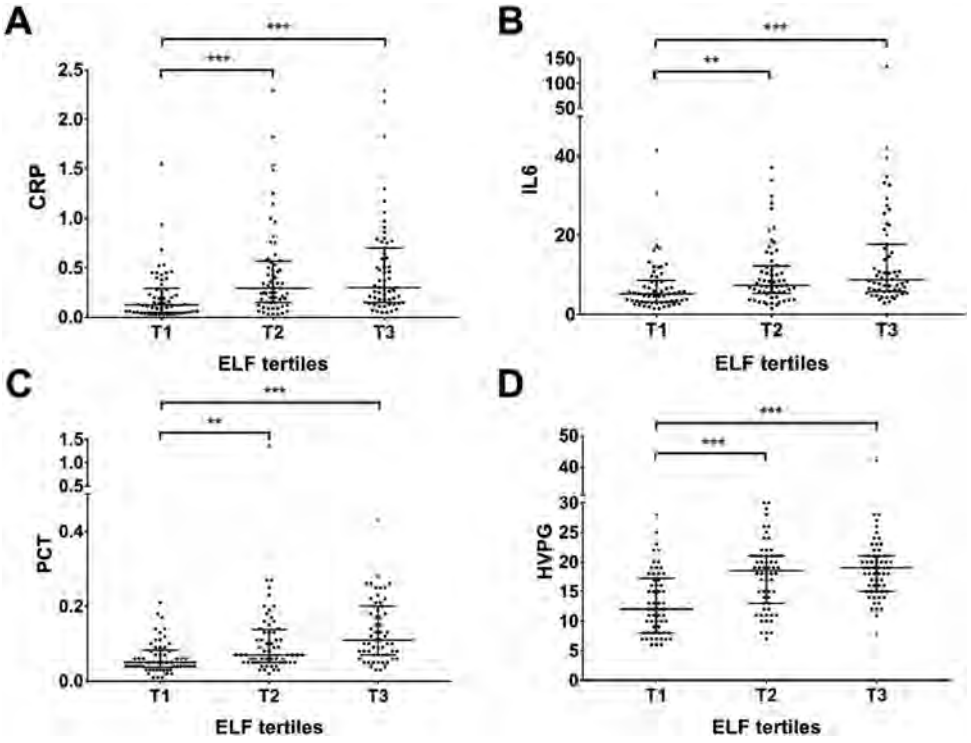

Figure: (abstract: SAT098)

systemic inflammation are linked to liver fibrogenesis in patients with advanced chronic liver disease (ACLD)/portal hypertension.

Method: ELF score, interleukin 6 (IL-6), procalcitonin (PCT), and C-reactive protein (CRP) were analyzed in 177 patients with a hepatic venous pressure gradient (HVPG) ≥6 mmHg recruited from the prospective VICIS study (NCT03267615). Patients with clinically stable ACLD and without pre- or post-hepatic portal hypertension, evidence of bacterial infection, hepatocellular carcinoma beyond Milan criteria, and history of liver transplantation were included.

Results: Serum levels of IL-6 (Spearman's $\rho = 0.358$; $P < 0.001$), PCT ($\rho = 0.486$; $P < 0.001$), and CRP ($\rho = 0.331$; $P < 0.001$) showed direct correlations with ELF score and stepwise increases with higher ELF tertiles (Figure; **P < 0.01 and ***P < 0.001).

Moreover, levels of IL-6 (6–9 mmHg: 5.45 [3.50–9.65] vs. 10–15 mmHg: 6.65 [3.44–12.48] vs. ≥16 mmHg: 7.75[5.34–13.76]; P = 0.015), PCT (6–9 mmHg: 0.06 [0.03–0.10] vs. 10–15 mmHg: 0.07 [0.04–0.16] vs. ≥16 mmHg: 0.09 [0.05–0.14]; P = 0.009), and CRP (6–9 mmHg: 0.19 [0.06–0.28] vs. 10–15 mmHg: 0.20 [0.08–0.41] vs. ≥16 mmHg: 0.29 [0.14–0.59]; P = 0.009) increased with portal hypertension severity. To investigate the association between markers of systemic inflammation and the dynamic process of liver fibrogenesis, we further stratified/adjusted our analysis by HVPG.

In patients with subclinical portal hypertension (i.e., HVPG 6–9 mmHg), only PCT showed a meaningful correlation with ELF. Interestingly, in patients with HVPG 10–15 mmHg/≥16 mmHg, IL-6 ($\rho = 0.304$; $P = 0.026$/$\rho = 0.353$; $P < 0.001$), PCT ($\rho = 0.488$; $P < 0.001$/$\rho = 0.406$; $P < 0.001$), and CRP ($\rho = 0.456$; $P = 0.001$/$\rho = 0.232$; $P = 0.020$) were directly correlated with ELF. Moreover, IL-6 ($B = 0.022$; $P = 0.006$) and PCT ($B = 7.841$; $P < 0.001$) were linked to ELF, even after adjusting for HVPG. Finally, IL-6, PCT, and HVPG were independent determinants of ELF in multiple linear regression analysis.

Conclusion: We observed a link between markers of systemic inflammation and ELF that is independent from portal hypertension severity, providing evidence for the role of bacterial translocation-induced inflammation as a key driver behind the dynamic process of liver fibrogenesis in humans.

SAT099

Rotational thromboelastometry (rotem)-based assessment of coagulopathy in cirrhotic patients stratified by severity of portal hypertension

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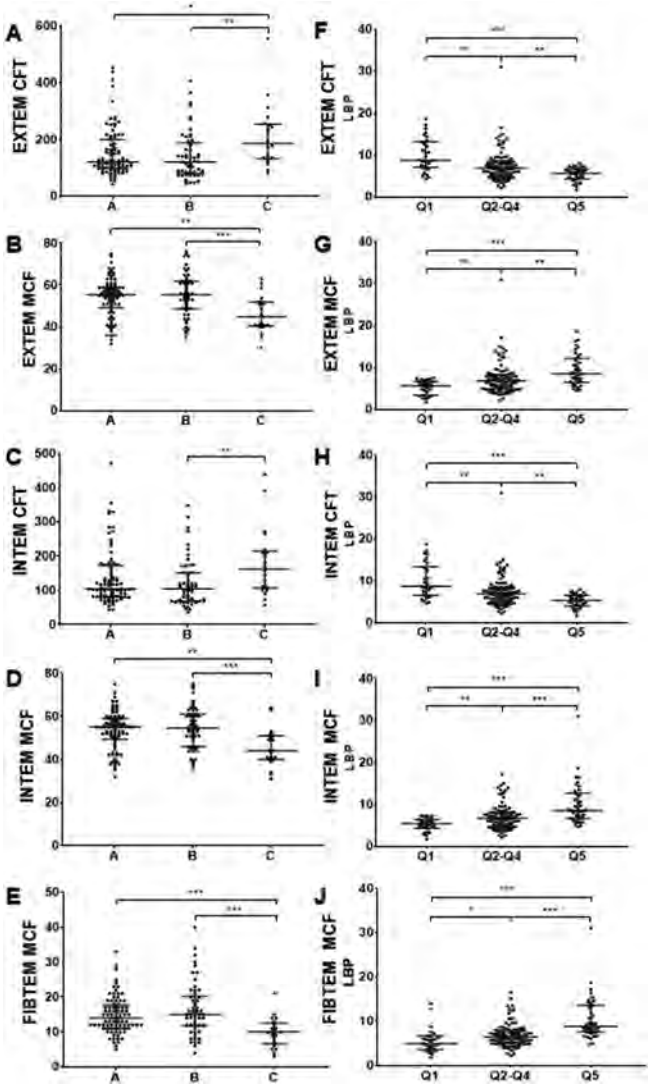
Background and Aims: Patients with advanced chronic liver disease (ACLD) exhibit complex coagulation disorders that confer increased risk for both bleeding and thrombosis. Conventional coagulation tests often do not reflect the hemostatic state. Rotational thromboelastometry (ROTEM) measures clot formation and dissolution in real-time. In this study, we systematically explored the impact of portal hypertension (PH) on ROTEM.

Method: ROTEM data, serum levels of C-reactive protein (CRP), procalcitonin (PCT), lipopolysaccharide binding protein (LBP), and epinephrine-stimulated platelet function assay (Epi-PFA) were analyzed in 159 consecutive patients with a hepatic venous pressure gradient (HVPG) ≥6 mmHg recruited from the prospective VICIS study (NCT03267615). Patients with clinically stable ACLD and without pre- or post-hepatic portal hypertension, hepatocellular carcinoma, or previous liver transplantation were included.



Results: Patients were stratified by PH severity, i.e. HVPG 6–9 mmHg vs. 10–19 mmHg vs. ≥20 mmHg. Neither EXTEM clot formation time (CFT, P = 0.804), EXTEM maximum clot firmness (MCF, P = 0.347), INTEM clotting time (CT, P = 0.561), INTEM CFT (P = 0.653), INTEM MCF (P = 0.271), or FIBTEM MCF (P = 0.921) differed between HVPG strata.

Child-C patients showed increased EXTEM CFT, INTEM CT, INTEM CFT, whereas EXTEM MCF, INTEM MCF, and FIBTEM MCF were significantly lower as compared to Child-A and/or Child-B patients (all P < 0.05; Figure A–E: *p < 0.05, **p < 0.01, ***p < 0.001).

In Child-A patients MCF progressively decreased with severity of PH (EXTEM MCF: 6–9 mmHg: 59 [54–68] vs. 10–19 mmHg: 56 [48–59] vs. ≥20 mmHg: 54 [45–58], P = 0.023; INTEM MCF: 6–9 mmHg: 57 [53–67] vs. 10–19 mmHg: 55 [48–59] vs. ≥20 mmHg: 52 [44–55], P = 0.009). Conversely, ROTEM results were similar in Child-B and Child-C patients across HVPG strata.

Patients with shortest CFT (EXTEM and INTEM, lowest quintile) had higher levels of LBP, CRP and PCT as well as shorter closing time on Epi-PFA (all P < 0.05). In line, serum levels of LBP (Figure F–J), CRP and PCT were higher and Epi-PFA closing time was shorter (all P < 0.05) in patients with highest MCF values (EXTEM and INTEM, highest quintile).

Conclusion: Results of ROTEM link the severity of portal hypertension to coagulation in compensated Child-A patients. Prolonged CFT and impaired MCF assessed by ROTEM are in agreement with previously reported bleeding tendencies in Child-C patients. Bacterial translocation and systemic inflammation are associated with a procoagulant state.

SAT100

Impact of extended- spectrum- beta- lactamase faecal carrier on cirrhotic patients: a retrospective study on clinical outcomes before and after liver transplantation

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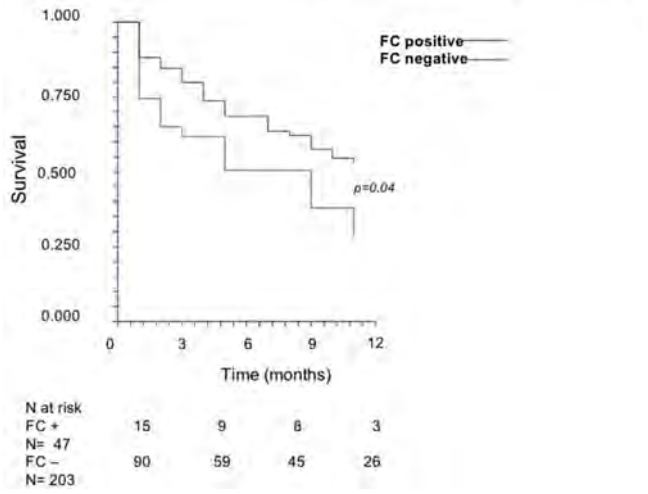
Background and Aims: Infections are very common in cirrhotic patients and are associated with an increased risk of liver failure and liver-related complications, especially, in patients awaiting liver transplantation (LT). It is known that pre-LT colonization with Methicillin-Resistant-Staphylococcus-Aureus (MRSA) or Extended-Spectrum-Beta-Lactamase (ESBL) bacteria is an independent risk factor for infections after LT. The aim of this study was to evaluate the impact of MRSA and ESBLE fecal carriage at 6 and 12 months on infections and liver-related complications (LRC) during waitlist and on infections after LT.

Method: We retrospectively included 250 of 483 cirrhotic patients that underwent to LT from December 2015 to January 2018 in our liver transplant center, screened for MRSA or ESBL colonization at nasal and rectal swab, at the time of waitlist inscription and after LT.

Figura 5. Liver-related-complications-free-survival on waitlist according to fecal carriage



Results: 76% of patients (n = 109) were male with mean age of 57.5 ± 10, the most frequent cause of liver disease was alcoholic (39%, n = 99). The median of MELD score was 19 (12–28). Only 1 patient was positive for MRSA. Nineteen percent of patients (n = 47) were fecal carriers (FC) at the moment of inscription on waitlist and 15% (n = 37) after LT. The most isolated germ was E. Coli (53%). Infection free-survival on waitlist and after LT, according to FC was not statistically different between two groups [HR: 1.5, 95%; p = 0.28);

[HR 0.99; p = 0.9]. LRC-free-survival at 6 and 12 months was significantly lower in FC vs. No FC [HR 1; p < 0.04)]. MELD score >19 [HR 3; (p = 0.01)] and occurrence of infection <3 months on waitlist [HR 4.13; (p < 0.001)] were independent risk factors for LRC occurrence at multivariate analysis.
Conclusion: Our study is the first showing, in a cohort of cirrhotic patients waiting for LT, that LRC-free survival is lower in FC, but infection free survival is not different in the two groups.

SAT101

A randomized, double-blind study to evaluate the safety and tolerability of KB174, a novel synthetic glycan, in patients with well-compensated cirrhosis

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Background and Aims: Microbiome Metabolic Therapies (MMT™) are proprietary ensembles of novel synthetic glycans that have the potential to reverse the dysbiosis associated with hepatic encephalopathy (HE) and reduce the gut contribution to blood ammonia levels, that could lead to improved clinical outcomes for patients with cirrhosis. The MMT KB174 has been shown to reduce microbiota-associated ammonia in *ex vivo* testing of microbiome samples from patients with cirrhosis. Lactose-[^{15}N]-ureide tracer has been used to model changes in nitrogen metabolism of the microbiome by measuring ^{15}N recovery in urine, stool, and blood.
Method: Patients with well compensated cirrhosis (Childs-Pugh A or Childs-Pugh B) were randomized and double-blinded, 1:1, to KB174 or maltodextrin, a digestible control substance. KB174 was titrated to a peak dose of 36g bid for a total treatment duration of 28 days.
Three days prior to randomization and three days prior to the end of dosing, patients received an amino acid challenge followed by 4.5 mg/kg nitrogen tracer. Safety was assessed from first dose of study product through the post intake follow up period. Urine, stool, and blood were collected for tracer, as well as measures of safety and tolerability (Gastrointestinal Questionnaire (GITQ) and Bristol Stool Scale (BSS)).
Results: Forty patients were randomized. Ten pts were enrolled who had liver disease but did not meet the entry criterion threshold for cirrhosis as measured by transient elastography. Adverse events were generally GI-related and mild to moderate in severity in both groups. One patient in each group had transient interruption of study product. There was one unrelated serious adverse event in a patient receiving KB174. Gastrointestinal tolerability measures showed only small changes (max 0.2–0.4 units for GITQ and BSS scores with no significant differences between groups).
Conclusion: This is the first clinical study to report the effect of KB174 in patients with cirrhosis. KB174 titrated up to 72 g was shown to be well tolerated with no clinically significant safety signals observed in patients with well-compensated cirrhosis.

SAT102

Renal clearance measured by iohexol identifies cirrhotic patients with normal creatinine at risk of serious adverse events

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Background and Aims: Renal dysfunction is a severe complication of advanced cirrhosis and even slight changes within normal serum creatinine are associated with greater morbidity and mortality. However, glomerular filtration rate (GFR) from creatinine leads to overestimation of renal function. Alternatively, GFR from exogenous substances is the gold standard for evaluation of renal function. However, there is a lack of data on its usefulness as predictors of the risk of serious adverse events (SAE). Our aims were to evaluate iohexol clearance as a predictive tool for SAE in cirrhotic patients with normal creatinine, and to identify characteristics associated with overestimation of GFR.
Method: Cirrhotic patients with normal creatinine (<1.4 mgr/dL) at the time of the study were offered to participate from May/2016 to Oct/2019. GFR was calculated in all patients from plasma clearance of creatinine and iohexol by dried blood spot method. The patients were grouped according to GFR-iohexol value: <90 ml/min (overestimated) and ≥90 ml/min (non-overestimated). Patients were followed up to identify hospital admissions and/or mortality defined as SAE.
Results: We included 125 patients (64.6 ± 8.2 years, 82% males): 76% alcoholic, Child 47% A, 42% B, 11% C, MELD 13.8 ± 5.3. Despite normal creatinine value (0.8 ± 0.2 mgr/dL), GFR was decreased (86.3 ± 28.3 ml/min). The overestimated group (n = 74) compared to the non-overestimated group (n = 51) was associated with: older age (65.9 vs 62.6 years; p < 0.024), female sex (26 vs 8%; p < 0.011), lower BMI (27 vs 30; p < 0.012), ascites (58 vs 37%; p < 0.038) and previous AKI (53 vs 28%; p < 0.005. In the multivariable model; female sex [OR: 4.06; 95% CI (1.29–12.77); p = 0.017], previous AKI [OR: 2.95; 95%CI (1.37–6.33); p = 0.006] and lower BMI [OR:0.89; 95%CI (0.81–0.98); p = 0.016] were predictors of overestimation. After a median follow-up of 18 [7–30] months, the overestimated group presented a higher rate of hospital admissions (43 vs 24%; p = 0.023), deaths (22 vs 14%; p = 0.26) and overall SAE (47 vs 29%; p < 0.045). In Cox regression model, the overestimated group presented higher risk of future admissions [HR: 2.24; 95%CI (1.15–4.37); p = 0.018] and SAE [HR: 1.94; 95%CI (1.06–3.58); p = 0.033].
Conclusion: Overestimation of renal function is associated with female sex, low BMI and previous AKI event. GFR with iohexol clearance allows the identification of cirrhotic patients with normal serum creatinine, at risk of SAE during follow-up.

SAT103

Clinical relevance of sarcopenia in liver transplant candidates

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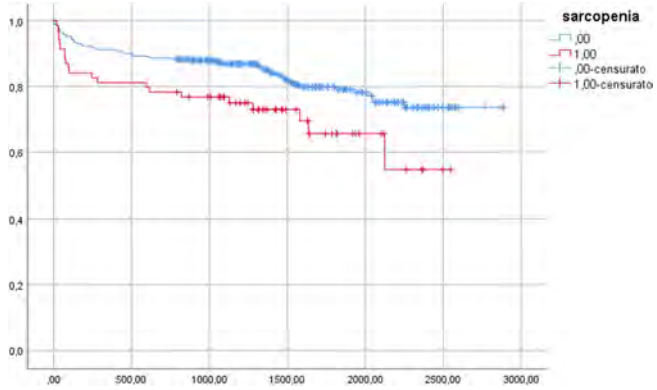
Background and Aims: Sarcopenia, characterized by loss of skeletal muscle mass, affects 30 to 70% of cirrhotic patients. Sarcopenia has recently emerged as an independent factor associated with elevated mortality in end-stage liver disease (ESLD) patients and liver transplant (LT) candidates. Few studies have assessed the impact of sarcopenia on peri-transplant and post-transplant outcomes. Our study aimed to investigate the association between sarcopenia and peri-transplant and post-transplant outcomes in LT candidates.
Method: 410 cirrhotic patients, who received a LT at Niguarda Hospital, from January 2012 to December 2016 were enrolled. Skeletal muscle index at the third lumbar vertebra was measured by CT scan, and sarcopenia was defined using previously published gender and BMI –specific cutoffs.
Results: 365 patients (69%) were male, with a median age at LT of 54 years. The most common etiologies of cirrhosis were HCV (52%), alcohol (16%) and autoimmune diseases (6%). Sarcopenia was diagnosed in 69 patients (16%), and was more frequent in those with refractory ascites (p = 0.000), and a higher MELD score at LT (p = 0.000). While on waiting list, sarcopenic patients were more frequently admitted to the hospital for episodes of acute decompensation (p = 0.05), bacterial infections (p = 0.000) and to ICU to manage major cirrhosis complications (p = 0.000). Sarcopenic patients had longer ICU (p = 0.001) and hospital stays (p = 0.002) after receiving LT and a higher rate of bacterial and fungal infections

(0.001) post-transplant. Moreover, MDR infections, especially caused by Klebsiella Pneumoniae Carbapenemase-producing (KPC) bacteria were more represented in sarcopenic patients (p = 0.014). The median survival after LT was 1282 days for sarcopenic and 1411 for non-sarcopenic patients (P = 0.016). At multivariate analysis, older age at LT and pre-LT sarcopenia as well as post-LT MDR infections, use of CRRT and prolonged ventilation in ICU were all independently associated with mortality.



Conclusion: Sarcopenia is one of the most common complication in patients with cirrhosis and it is predictive of longer hospital stays, higher risk of waiting-list complications and post-LT bacterial infections, including MDR infections, and is associated with increased mortality after-LT.

SAT104

Impact of non-selective beta-blockers on hepatic encephalopathy in patients with liver cirrhosis

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Background and Aims: Non-selective β-blockers (NSBB) are routinely used for the treatment of portal hypertension and gastro-oesophageal varices in patients with liver cirrhosis; however prospective studies investigating the potential link between NSBBs and hepatic encephalopathy (HE) are still scarce. We investigated the relationship between NSBBs use and the presence of covert HE (CHE) as well as its potential association with the development of overt HE (OHE).

Method: In- and outpatients with an established diagnosis of liver cirrhosis treated between March 2017 and December 2018 at the University Medical Centre Mainz and the Diakonie Klinikum Siegen were included into this prospective cohort study and followed for a median of 364 days. Exclusion criteria were an OHE episode during the previous three months, current alcohol abuse, intake of psychotropic drugs, TIPSS, HCC or any active infection. CHE was diagnosed at study inclusion by pathological results in PHES. Predictors for the presence of CHE or the development of OHE during follow-up were analyzed using logistic regression or cox-regression models.

Results: 368 patients were screened and 224 finally included into the study. Median age was 60 years (IQR 52; 66). 56.7% were male and most patients had compensated stage of liver cirrhosis (Child A, B, C; 59%, 32%, 9%; Median MELD: 10). CHE was detected in 33.9% (n = 76) of patients at study inclusion and 39.3% (n = 88) were NSBB users. On logistic regression analysis, NSBB use (OR 1.88, 95% CI 1.03–3.42, p = 0.040), higher MELD score and a history of OHE were independently associated with the presence of CHE. Cumulative incidence of OHE was significantly higher in NSBB users than in non-users (p < 0.001). On cox-regression model, NSBB use (OR 3.07, 95% CI 1.66–6.56, p = 0.001), presence of CHE, lower albumin and higher MELD score were independently associated with the development of OHE.

Conclusion: NSBB use due to portal hypertension was associated with the presence of CHE as well as the development of OHE. Uncritical NSBB use should be avoided in patients with liver cirrhosis.

SAT105

Characterization of alterations in mechanical, thermal and pain sensitivity in cirrhotic patients with minimal hepatic encephalopathy

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Background and Aims: Hepatic encephalopathy (HE) associated to cirrhosis is a complex neuropsychiatric syndrome. Near 40% of cirrhotic patients have minimal hepatic encephalopathy (MHE) with mild motor and cognitive impairments.

Cirrhotic patients may have alterations in the peripheral nervous system, such as somatosensory perception. The perception of cold and heat pain is mediated by A-delta nerve fibers (myelinated, small diameter) and non-myelinated C fibers, respectively. The vibration is transmitted by myelinated larger diameter fibers (A-alpha). Alterations in thermal sensitivity have been described in patients with HE, which correlated with the degree of HE and with attention deficits.

The aim of this study is the evaluation and characterization of thermal sensitivity, vibration and heat-pain in cirrhotic patients and healthy controls, and to assess whether there are alterations associated to MHE.

Method: Sixty-five cirrhotic patients were included in the study, 41 without MHE and 24 with MHE, according to the PHES score (Psychometric Hepatic Encephalopathy Score) and 35 healthy controls. Selective and sustained attention were assessed using the Stroop and d2 tests. The evaluation and characterization of sensory thresholds was performed by quantitative sensory testing using a CASE IV device. The following sensory thresholds were measured: vibration detection threshold, which evaluates thick myelinated nerve fibers (A-alpha); cold detection threshold, which allows measurement of myelinated fine nerve fibers (A-delta) and heat-pain detection threshold that evaluates non-myelinated C fibers. The tests were performed on hand and foot.

Results: Results show that the thresholds of vibration and detection of cold in the foot are significantly higher in patients with MHE compared to those without MHE. This hyposensitivity correlates with attention deficits. Likewise, the reaction time is significantly longer in the tests of cold perception and heat pain when comparing patients with and without MHE. Finally, the total sum of the tests performed

out of the normal range by cirrhotic patients shows more significant differences with the control group when the hand is the test site, although the foot seems to be more affected by the presence of MHE.
Conclusion: Patients with MHE have a general decrease in cognitive and sensory abilities. Quantitative sensory tests could be used as an indicator of MHE and would allow studying the effects on the sensory system before and after a treatment.

SAT106

Role and prognostic value of routine doppler sonography in patients with severe liver disease - a prospective cohort study in an intensive care unit

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Background and Aims: Chronic liver disease is one of the major causes of morbidity and mortality. Inflammatory processes of the liver lead to hepatocellular damage and fibrosis of liver tissue. Due to the increase of resistance, hemodynamics of hepatic blood vessels alter. Ultrasound examination is of great importance in the evaluation of liver diseases. However, there is no sufficient data examining the precise role and prognostic value of routine Doppler sonography of liver perfusion in patients with severe liver disease. This study aims to determine the relation of the altering hepatic perfusion with the outcome of patients with severe liver disease in context of an intensive care treatment.
Method: Fifty patients with severe liver disease hospitalized in the internal intensive care unit of the Department of Internal Medicine I of the University Hospital Regensburg were examined with sonography at least twice a week. Liver perfusion was quantified by means of Doppler ultrasound to determine the hepatic artery resistance index (HARI) and the maximum portal vein velocity (PVv). For each patient the MELD (Model for End-Stage Liver Disease) score was calculated at the time of the study. In addition, clinical data such as the current catecholamine dose, the mean arterial blood pressure, ventilation and laboratory parameters were collected. Finally, the collected data, the duration of the intensive care treatment and the outcome of the patients were correlated with sonographic parameters.
Results: Analyses of the MELD score, the HARI and the maximum PVv in a scatter plot showed a linear, positive correlation between HARI and MELD score and a linear, negative correlation between maximum PVv and MELD score. Initial regression analyses quantify these correlations with a R2-value of 0,220 (HARI - MELD score) and 0.078 (PVv - MELD score). Furthermore, it appeared that the HARI increased in deceased patients on average by 1.6% with each examination, whereas it declined by 0.3% in non-deceased patients. On average, with each examination the maximum PVv increased by 1.8% in deceased patients and by 16.5% in non-deceased study participants.
Conclusion: The correlations of HARI and maximal PVv with the MELD score show that the development of liver perfusion is a prognostic factor. The routine assessment of HARI and the maximum PVv in patients with severe liver disease in the ICU should be further evaluated.

SAT107

Lack of evidence of significant tubular injury in patients with cirrhosis and persistent hepatorenal syndrome. implications for liver transplantation

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Background and Aims: Hepatorenal syndrome (AKI-HRS) is a distinctive form of AKI that occurs in patients with advanced cirrhosis characterized by striking renal vasoconstriction in the setting of preserved tubular function. However, information on the status of kidney tubules in AKI-HRS is scarce and controversy exists as to whether persistent severe renal vasoconstriction leads to tubular injury. The aim was to assess the possible development of tubular injury during the natural course of AKI-HRS by assessing changes in urinary levels of neutrophil gelatinase-associated lipocalin (NGAL) and interleukin-18 (IL-18), markers of tubular injury.
Method: We analyzed a cohort of 48 patients prospectively collected from patients admitted to hospital for management of complications of cirrhosis, 22 with AKI-HRS and 26 with acute tubular necrosis (ATN). Only patients meeting the criteria of type-1 HRS were included. Urine was collected from all patients at diagnosis of AKI, and at days 3, 7, and 14 during hospitalization.
Results: Patients with AKI-HRS had advanced cirrhosis with markedly impaired liver and renal function tests. Eleven of the 22 (50%) patients had resolution of AKI-HRS during hospitalization; by contrast, in the remaining 11 patients there was no resolution of AKI-HRS. There were no significant differences between patients with resolution vs persistent AKI-HRS with respect to baseline characteristics. However, 3-month mortality was markedly higher in patients with persistent AKI-HRS (64% vs 9%, persistent vs resolution; $p = 0.026$). There were no significant differences in NGAL levels between the two subgroups at any time point studied. By contrast, urinary NGAL levels were remarkably higher throughout hospitalization in patients with AKI-ATN. The highest NGAL value among patients with persistent AKI-HRS at day ≥ 3 was 458 μg/g, but value in that particular patient decreased to <50 μg/g at day 14. All other NGAL values available in these patients were <200 μg/g, lower than those in patients with AKI-ATN. There were no significant differences in urinary IL-18 between the subgroups.
Conclusion: There is no evidence of development of significant tubular injury during the course of AKI-HRS, at least during a 14-day period, even in patients with persistent AKI-HRS. These findings may have important implications in management of patients with cirrhosis and AKI, particularly in the context of liver transplantation.

SAT108

Hepatic and splenic elastography: are they predictors of recurrence of esophageal varices after complete eradication?

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Background and Aims: Endoscopic variceal surveillance combined with prophylactic banding decreases the incidence of variceal bleeding and it should be performed annually after successful eradication of esophageal varices (EV). The aim of this study was to assess which variables can be predictors of recurrence of EV after eradication, especially hepatic elastography (HE) and splenic elastography (SE), allowing to identify patients who may benefit from endoscopic control every two years.
Method: We retrospectively reviewed 99 consecutive patients who had complete eradication of EV after band ligation and underwent endoscopic surveillance for recurrence of EV or gastric varices, between February 2017 and October 2019. At time of control, HE and SE were performed and blood tests and abdominal ultrasound results were registered.

Results: Most patients were male n = 70 (70.7%). Mean age was 62.2 ± 10.5 years and mean body mass index (BMI) was 25.1 ± 8.1 Kg/m^2. The etiology of portal hypertension was cirrhosis in 87 (87.9%) patients and cavernoma in 12 (12.1%). Cirrhotic patients were mainly Child Pugh class A (92%) and had a mean MELD-Na$^+$ value of 10.7 ± 3.4 points. Concomitant beta-blocker therapy was observed in 68 (68.7%) patients. Mean value of hepatic elastography was 29.7 ± 20.6 kPa and mean value of splenic elastography was 69.7 ± 10.5 kPa.
Median time between complete eradication and endoscopic surveillance was 10 (1–1412) months. Recurrence of EV occurred in 25 (25.3%) patients, mainly small varices (n = 22). Gastric varices were observed in 12 (12.1%) patients, half of them with IGV1 type (n = 6). There was no statistically significant difference between patients with and without recurrent EV with respect to the following variables: age (p = 0.058), BMI (p = 0.458), time between eradication and control (p = 0.464), concomitant therapy with beta-blockers (p = 0.160), Child Pugh class (p = 0.329), MELD-Na$^+$ score (p = 0.643), ascites (p = 0.649), HE (p = 0.834) and SE (p = 0.986).
Conclusion: In this sample, most of patients who had recurrence of EV presented with small varices which suggest that these patients might benefit from a longer interval time between endoscopic surveillance (two years). Our study results suggest that hepatic and splenic elastography cannot replace upper endoscopy yet and patients with complete variceal eradication still need endoscopic screening.

SAT109

Risk of contrast-induced acute kidney injury in cirrhotic patients undergoing computed tomography: myth or reality?

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Background and Aims: Cirrhotic patients have been considered at increased risk for iodinated contrast-induced acute kidney injury (CI-AKI), but evidence is scant, mainly encompassing retrospective studies with conflicting results. Our study aimed at clarifying the existence of an increased risk of CI-AKI in cirrhosis.
Method: An observational retrospective and a subsequent prospective study were undertaken, evaluating all the patients hospitalized from January 2018 to October 2019. Three cohorts were compared: cirrhotics (A) and non-cirrhotics (C) undergoing contrast-enhanced CT scan (CECT) and cirrhotics not exposed (B) to intravenous iodinated contrast media (ICM). Kidney function parameters were analyzed at T0 (24–48h before CECT for cohorts A/C; at enrollment for B) and after 2, 5 and 7 days (T1). CI-AKI was defined according to KDIGO criteria. Patients with any potential cause of impairment of clinical stability and of serum creatinine (sCr) increase between T0 and T1 were excluded.
Results: Overall, 294 patients were enrolled: 83, 95 and 116 in cohort A, B and C, respectively. CI-AKI incidence in cohort A did not differ from C (2.4 vs 2.6%, p = 0.48) or B (2.4 vs 1%, p = 0.94). All cases were stage 1a, except 1 case stage 1b, and all regressed spontaneously in few days. Mean sCr and eGFR (MDRD-4) did not change significantly after CECT neither in cohort A (T0 vs T1: sCr = 0.8 ± 0.3 vs 0.8 ± 0.2 mg/dl, p = 0.81; eGFR = 108 ± 38 vs 105 ± 32 ml/min/1.73 m^2, p = 0.29) nor C (T0 vs T1: sCr = 0.8 ± 0.2 vs 0.8 ± 0.3 mg/dl, p = 0.29; eGFR = 97 ± 33 vs 100 ± 34 ml/min/1.73 m^2, p = 0.16). In a subgroup of 69 consecutive cirrhotic patients urinary NGAL was measured, showing no significant changes from T0 to T1 in any patient neither in cohort A (26 ± 20 vs 24 ± 23 ng/ml, p = 0.48) nor B (30 ± 34 vs 31 ± 30 ng/ml, p = 0.86).
Conclusion: Cirrhosis per se does not appear to increase the risk of CI-AKI after CECT compared to the general population. AKI episodes were mild, rapidly reversible, with comparable incidence between CECT and non-CECT patients, hence likely attributable to spontaneous sCr fluctuations rather than to ICM. Even the assessment of NGAL, a sensitive marker of tubular damage, could not detect any sign of acute kidney injury after ICM exposure.

SAT110

Flash glucose monitoring system: a required tool to improve glycaemic control in patients with liver cirrhosis

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Background and Aims: Blood glucose dynamics in Liver Cirrhosis (LC) has been scarcely studied, however marked glycaemia fluctuations appear to be frequent, with a higher risk of postprandial hyperglycaemia and nocturnal hypoglycaemia, which are easily undervalued by standard monitoring tools. Flash glucose monitoring system (FGMS) is an improved subset of Continuous glucose monitoring with a recognized effectiveness on glycaemic control, recently validated by our group as a suitable option for monitoring Diabetes Mellitus (DM) in patients with LC. We aimed to characterize the glycaemic profile of this population and assess the clinical applicability of FGMS.
Method: A prospective, case-control study was performed in 61 ambulatory patients with LC and DM (LC, n = 31) or Type 2 DM (T2DM, n = 30). For 14 days, patients performed 4 assessments per day of self-monitoring of blood glucose (SMBG) followed by FGMS scanning (scheduled upon waking, 2 hours after the beginning of lunch and dinner and at bedtime). For a complete 24-hour glycaemic profile, a FGMS scan was performed once every 8 hours. Clinical and biochemical data were assessed, including the glycated haemoglobin (HbA1c).
Results: Patients with LC revealed significantly lower fasting glucose levels (p < 0.001), though no significant differences were detained regarding postprandial hyperglycaemia. The number of hypoglycaemia events were similar between the groups (p = 0,7), nonetheless a higher number of nocturnal hypoglycaemia episodes were detected in patients with LC (p = 0,008). FGMS recognized hypoglycaemia events in about 75% of the patients in LC group (median = 4; average duration 126 minutes) and SMBG exhibited a significantly lower hypoglycaemia detection rate (43,5%; p = 0,04). Most patients with LC revealed a normal value of HbA1c (median 6,0; IQR 2,0), which displayed a moderate correlation with postprandial hyperglycaemia ($\rho = 0.5$; $p < 0.001$) and no correlation with hypoglycaemia events ($\rho = -0.4$; $p = 0.07$).
Conclusion: Comparing to the standard tools (SMBG and HbA1c), FGMS revealed a greater performance in patients with LC, exhibiting a higher hypoglycaemia detection rate, mainly nocturnal hypoglycaemia events, frequently noticed in this population.

SAT111

Incorporation of frailty estimated by gait speed within MELD and the predictive potential for mortality in cirrhosis

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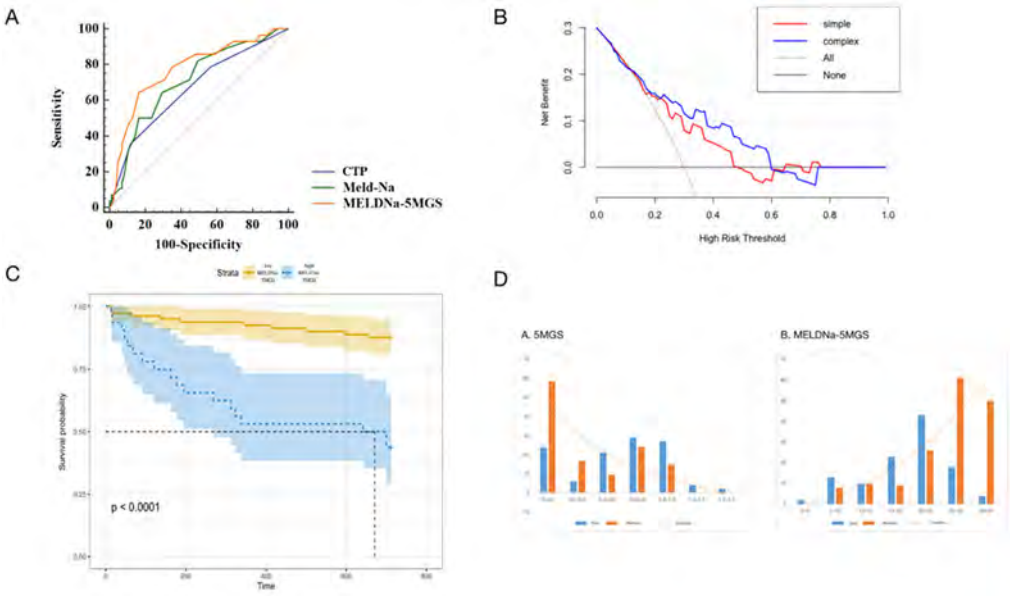

Figure: (abstract: SAT111)

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Background and Aims: The five-meter gait speed (5MGS), a simple and reliable performance metric and surrogate indicator of frailty, consistently predicts adverse events in elders. Additionally, MELD-Na score fails to capture nutritional and functional decline of cirrhotic patients which may confer excess mortality. We hypothesized that 5MGS might be associated with all-cause mortality and inclusion of frailty assessment within MELD-Na could improve the prediction of mortality in cirrhosis.
Method: 5MGS were measured at baseline in 113 hospitalized cirrhotic patients. Survival status over two years and cirrhosis-related complications were recorded. We evaluated the prognostic value of 5MGS (as a continuous variable and as a dichotomous variable). The definition of slow versus preserved 5MGS was 0.8 ms^{-1} based on previous publication. Using Cox proportional hazards regression, a novel MELD-5MGS score was derived. ROCs estimated discrimination between new score model and established prognostic indices.
Results: The Continuous 5MGS and slow 5MGS were independent predictors of all-cause mortality (5MGS: HR 0.133 (0.047 to 0.347), $p < 0.001$; slow 5MGS: HR 4.805 (1.536 to 15.026), $p < 0.007$). The equation derived from Cox regression analysis was as follows: MELDNa-5MGS: MELD-Na score + 11 × slow 5MGS. Two-year mortality in patients with high MELD-5MGS score was significantly higher ($p < 0.001$). The discriminatory power was significantly better for MELDNa-5MGS than MELD-Na score (AUC: 0.802 vs 0.724, $p = 0.014$ for 12-month; 0.773 vs 0.709, $p = 0.044$ for 24-month).
Conclusion: In cirrhotic patients, 5GMS is an independent risk factor of mortality. Modification of MELD-Na to include frailty estimated by low 5GMS is related to improved prognostication of mortality.

SAT112

Serologically assessed fragments of type VI collagen are predictors of progression free survival and death in patients with hepatocellular carcinoma

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Background and Aims: Serum alpha-fetoprotein (AFP) has suboptimal performance in the screening of hepatocellular carcinoma (HCC). During liver fibrosis and HCC development, collagen derived neoepitope fragments are released into circulation. Clinically, type VI collagen (COL6) a3 is known to relate to fibrosis, apoptosis and cell proliferation in HCC. We tested the ability of C6M a marker of matrix metalloprotease degradation of the a1 chain and PRO-C6 a COL6 formation marker of the a3 chain also known as the signaling fragment endotrophin (ETP) produced by fibroblasts, to predict outcome in HCC.
Method: Plasma C6M and PRO-C6 were assessed in 1) 86 biopsy-proven HCC patients, 2) 86 age and sex-matched cirrhotics, 3) 86 non-cirrhotics, and 4) 86 healthy controls. Data for clinical characteristics, liver related biochemistry and AFP were collected. Survival data were collected for up to 17-years after cirrhosis diagnosis. Progression free survival (PFS) was defined as time from diagnosis to tumor progression or death in HCC patients; overall survival (OS) was defined as all-cause mortality. Biomarker relations to survival was calculated by Kaplan-Meier analysis using median or quartiles(Q) as cut-off and by Cox Regression analysis.
Results: C6M was significantly related to disease severity ($p < 0.01$), however did not display significant difference between groups 1–4. In contrast, PRO-C6 was able to separate groups 2–4 from HCC patients ($p < 0.0001$, $p < 0.0001$ and $p = 0.007$, respectively). During follow-up, 75% of the cirrhotic patients experienced progression. Neither, $C6M_{median}$ or $C6M_{Q4vsQ1}$ were able to predict PFS, however were able to predict OS (median: Hazard Ratio (HR) = 2.4, $p = 0.02$; Q4 vs Q1-3: HR = 2.9, $p = 0.03$). $PRO\text{-}C6_{median}$ and $PRO\text{-}C6_{Q4vsQ1\text{-}3}$ were significantly associated with time to PFS (median: HR = 1.9, $p = 0.01$; Q4 vs Q1-3: HR = 2.3, $p = 0.01$) and to OS (median: HR = 2.4, $p = 0.003$; Q4 vs Q1-3: 3.2, $p = 0.004$). In comparison, AFP above the recommended cut-off (20 IU/mL) provided a HR = 1.87 ($p = 0.02$) for PFS and HR = 3.0 ($p = 0.002$) for OS. Only PRO-C6 was significant in a COX model including PRO-C6 and AFP for PFS (HR = 1.06 per unit change, $p = 0.020$). Both PRO-C6 and AFP were significant for OS (PRO-C6: HR

= 1.08 per unit change, p = 0.007; AFP: HR = 1.00 per unit change, p = 0.017).
Conclusions: Markers of COL6 relate to disease severity in patients with hepatic fibrosis and HCC. C6M, ETP and AFP were associated with progression and overall survival; while ETP was superior.

SAT113
Mechanical ventilation in patients with hepatopulmonary syndrome: prevalence, resource utilization, and prognosis: a nationwide analysis

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Background and Aims: Hepatopulmonary syndrome (HPS) is a frequent complication of liver cirrhosis, and liver transplantation is the only definitive therapy. Patients with HPS are often hospitalized with respiratory failure requiring invasive mechanical ventilation (IMV). There is limited data on the prevalence and hospital-related outcomes for these patients. We aimed to investigate the prevalence, resource utilization, and prognosis of patients with HPS requiring IMV.

Table: Demographics and outcomes of interests in patients with HPS with and without IMV

	HPS with MV *n* or *(%)*	HPS without MV *n* or *(%)*	*p* value
No. of patients	841	4794	
Patient Characteristics			
Female	357 (42.52%)	2384 (49.74%)	<0.001
Age in years (Mean)	56.73	56.27	<0.001
Race			<0.001
White	74.64	70.79	
Black	4.92	5.72	
Hispanic	14.84	17.52	
Other			
Charleston comorbidity index			<0.001
0	1.19	1.36	
1	3.51	7.79	
2	6.99	9.44	
3 or more	88.31	81.42	
Hospital Characteristics			
Hospital Teaching Status			<0.001
Teaching	21.2	22.35	
Non-Teaching	78.8	77.65	
Hospital size			<0.001
Small	8.91	9.98	
Medium	17.89	20.45	
Large	73.2	69.57	
Hospital Region			<0.001
Northeast	12.85	18.21	
Midwest	24.16	22.72	
South	28.46	34.1	
West	34.53	24.97	
Primary and Secondary Outcomes			
Total Hospitalizations	841	5,636	
Mortality n (%)	427 (50.77%)	310 (5.50%)	
Mean Length of Stay (Days)	15.77	8.9	
Mean Hospitalization Charges (USD)	279,012$	106,365$	

Method: We used the National Inpatient Sample (NIS) to identify patients with HPS who required IMV through ICD 9 CM codes between 2012–2014. Primary outcome included the rate of IMV requirement and secondary outcomes were inpatient mortality, length of stay (LOS) and hospitalization charges. We also used univariate and multivariate regression models to adjust for confounders to identify predictors of mortality.
Results: A total of 5,636 non-elective admissions were recorded for HPS between 2012–2014. Out of these, 2,739 (48.59%) patients presented with acute respiratory failure, and 14.92% patients required IMV. The mean age of patients requiring IMV was 56 years, 42.52% were females, and 74.64% were Caucasians (Table). The mortality among patients requiring IMV was 50.77% (427/841). Mean time to start IMV was recorded as 3.85 days. Patients in the IMV group had increased mean LOS 15.77 vs. 8.9 days, increased mean total hospitalization charges 279,012$ vs. 106,365$. We also found that IMV (OR 6.25, p < 0.01), age (OR 1.02, p = 0.04), acute kidney injury (2.81 p = 0.00), acute respiratory failure (3.2, p < 0.01) and sepsis (OR 2.76, p = 0.01) are independent risk factors for mortality in IMV group.
Conclusion: Our study shows that a large number of hospitalized patients with HPS will require IMV which is associated with resource utilization, and exceptionally high (51%) mortality. The requirement for IMV is an independent predictor for poor prognosis, and eligible patients should be prioritized for liver transplant allocations.

SAT114
Acute kidney injury: a predictor of worse outcomes in variceal bleeding

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Background and Aims: Variceal Gastrointestinal Bleeding (VGIB) is a life-threatening emergency that can lead to significant morbidity and mortality. These patients are at risk of developing acute kidney injury (AKI) from inadequate fluid resuscitation due to the fear of third spacing. We aimed to investigate the prevalence and impact of AKI on in-hospital mortality and resource utilization in VGIB.
Method: We identified the patients with VGIB who had co-existing diagnoses of AKI using the ICD-9 CM codes in the National Inpatient Sample (NIS) database between 2009–2014. Primary outcome included the prevalence of AKI in VGIB with secondary outcomes as inpatient mortality, length of stay (LOS), total hospitalization charges, need for transfusion and mechanical ventilation, and prevalence of shock. We adjusted for confounding factors by performing univariate and multivariate regression models to identify predictors of mortality in these patients.
Results: A total of 23,314 VGIB related hospitalizations were identified, out of which 3,197 (13.71%) had AKI. Patients in this group were older (mean age 60.37 vs. 56.54 years) with a predominance of Caucasian males. In total, 1,360 patients died during the same admission, with 585 (43.01%) had co-existing AKI. These patients had higher mean LOS (6.8 vs. 4.68 days) as compared to the control group. Similarly, the inflation-adjusted mean total hospitalization charges (79,050$ vs. 42,520$) and cost (20,917$ vs. 11,729$) were also higher. After adjusting for confounding factors, AKI was turned out to be an independent predictor of mortality with aOR of 5.53 (p-value: <0.001 95% CI: 4.07–7.50).
Conclusion: Our study showed that AKI is an independent predictor for inpatient mortality and increased resource utilization in VGIB. Adequate volume resuscitation can prevent AKI and improve these outcomes.

Table: (abstract: SAT114) Demographics and outcomes associated with VGIB with and without AKI

	Acute VGIB with AKI *n* or *(%)*	Acute VGIB without AKI *n* or *(%)*	*p* value
Total hospitalizations	3,197 (13.71%)	20,117 (86.29%)	
Patient Characteristics			
Female	923 (28.87%)	6263 (31.13%)	<0.001
Age in years (Mean)	60.37	56.64	<0.001
Race			<0.001
White	60.98	67.69	
Black	12.7	6.9	
Hispanic	18.26	18.05	
Other	8.06	7.36	
Hospital Characteristics			
Hospital size			<0.001
Small	11.16	13.81	
Medium	29.31	27.5	
Large	59.53	58.69	
Hospital Location			<0.001
Rural	1.16	9.79	
Urban	112.59	76.46	
Hospital Region			<0.001
Northeast	13.76	14.83	
Midwest	22.63	20.76	
South	39.62	38.14	
West	23.99	26.27	
Primary and Secondary Outcomes			
	Adjusted Odds Ratio (aOR) or coefficient	**p-value**	**95% Confidence Interval**
Mortality	5.53	<0.001	4.07–7.50
Length of Stay	2.163	<0.001	1.55–2.76
Total Hospitalization Charges	34,681	<0.001	26,083–43,280
Complications			
RBC transfusion	1835 (57.41%)	9, 368 (46.56%)	
Mechanical Ventilation	863 (26.99%)	1,685 (8.37%)	
Hypovolemic Shock	470 (14.71%)	943 (4.68%)	

SAT115

The prospective prognostic values of diabetic conditions based on 75g oral glucose tolerance test in cirrhotic patients

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Background and Aims: Disorders of glucose metabolism, such as impaired glucose intolerance (IGT) and diabetes mellitus (DM), occur frequently in cirrhosis. However, DM and IGT have not received enough attention and have been underestimated when fasting plasma glucose (FPG) levels are considered. we evaluated whether abnormal glucose metabolism, estimated by FPG and the oral glucose tolerance test (OGTT), influences the prognosis of patients with liver cirrhosis.
Method: This prospective observational study included 713 patients with either compensated or decompensated cirrhosis; these patients underwent a 75-g OGTT. The patients were divided into three groups: patients with normal glucose tolerance (NGT), patients with IGT ($100 \leq$ FPG < 126 mg/dL or $140 \leq$ 2-h OGTT < 200 mg/dL), and patients with newly diagnosed DM ($126 \leq$ FPG or 200 mg/dL $\leq$2-h OGTT).
Results: Among 713 patients, NGT was diagnosed in 139 (19.5%), IGT in 252 (35.3%), and DM in 322 (45.2%). During a median follow-up period of 42.0 months (interquartile range, 20.5–66.5 months), the cumulative survival rates of patients were as follows: NGT, 75.6%; IGT, 57.6%; and DM, 54.8%. Overall, IGT [adjusted hazard ratio (aHR) = 1.669; 95% CI = 1.050–2.653; P = 0.03] and DM (aHR, 1.723; 95% CI = 1.101–2.698; P = 0.017) were identified as independent predictors of mortality after adjustment for Child–Turcotte–Pugh (CTP) and MELD scores. In patients with compensated cirrhosis (CTP class A; n = 415), neither IGT nor DM conferred a higher risk for mortality. However, among patients with decompensated cirrhosis (CTP class B and C; n = 298), those with IGT (aHR, 2.279; P = 0.022) and DM (aHR, 2.211; P = 0.022) showed a worse survival rate than those with NGT. In addition, DM was identified as an independent risk factor for acute kidney injury (aHR, 2.247; P = 0.036) and infection (aHR, 2.801; P = 0.034).
Conclusion: Abnormal glucose tolerance in patients with IGT or DM is associated with an unfavorable prognosis in patients with cirrhosis, particularly in the decompensated state. Also, our results demonstrated that AKI and infection were more frequent in patients with DM than in those with NGT.

SAT116

PROSPER study reveals reduction in bed days per hospitalisation and decreased risk of mortality for patients observed on rifaximin-alpha 550mg compared to a cohort on standard of care

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Background and Aims: To provide real-world evidence on the effectiveness of rifaximin-alpha 550 mg (rifaximin) treatment in patients with persistent hepatic encephalopathy (HE) to reduce mortality and time in hospital compared to those patients who do not receive rifaximin (noted as standard of care (SOC), majority receiving lactulose alone).
Method: The Prospective Real World Outcomes Study of Hepatic Encephalopathy Patients' Experience on Rifaximin-α (PROSPER) clinical trial was a multinational, multicentre, observational study conducted under real-world clinical practice conditions combining a retrospective with a prospective approach. The study was conducted in centres in Australia, Belgium, Denmark, France, Germany, Netherlands, Sweden, Switzerland and UK. Patients with cirrhosis and persistent HE were enrolled, with a total of 389 observed cases. Management of patients remained unchanged beyond clinical practice. Patients underwent prospective observation for a minimum of 12 months and in some cases up to 26 months. The number of HE-related bed days, the number of bed days per hospitalisation, and the relative risk of mortality were compared between patients who received rifaximin versus patients who received SOC.
Results: The efficacy analysis set contained 280 cases in the rifaximin cohort and 89 cases in the SOC. The rifaximin treatment group had clinically meaningful advantages compared to the non-rifaximin group in all three performed analyses: HE-related bed days were reduced from (mean, 95% CI) 10.80 (9.12, 12.78) to 4.24 (2.95, 6.09) pre- and post-study enrolment respectively whereas the non-rifaximin cohort remained relatively stable at 9.72 (7.11, 13.29) and 9.56 (4.16, 21.94) pre- and post-study enrolment respectively. A comparison between these cohorts showed 60% benefit for the rifaximin cohort compared to SOC. Further post hoc analysis of bed days per hospitalisation event showed a 87% risk reduction in favour of rifaximin 550mg. Risk of mortality is significant for patients with HE and observations in these cohorts showed a relative risk reduction for patients taking rifaximin 550mg which ranged from 39% in the overall cohort and as high as 80% in selected high recruiting sites.
Conclusion: Descriptive comparisons between rifaximin and SOC cohorts highlighted demonstrable benefits for number of HE-related bed days, bed days per hospitalisation and a clinically meaningful reduction in mortality for patients taking rifaximin 550 mg.

SAT117

Hemodynamic effects of direct-acting antivirals in patients with hepatitis-C virus-associated cirrhosis and portal hypertension non responsive to beta-blockers

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Background and Aims: Hemodynamic non-responders to non-selective β-blockers (NSBBs) are at high risk of unfavorable outcomes. Safe therapies to rescue non-responders are scarce. Whether etiologic treatment may achieve an additional decrease of portal pressure in these patients has not been clarified. Direct-acting antivirals (DAA) are safe and effective in patients with hepatitis-C virus-associated cirrhosis (HCV-cirrhosis) and offer a chance to clarify this issue. The present study aimed to assess the effect of DAA on portal hypertension (PH) in patients with HCV-cirrhosis and clinically significant PH (CSPH), according to the previous hemodynamic effect of chronic therapy with NSBBs.
Method: We performed an observational cohort study of patients with HCV-cirrhosis and CSPH treated with NSBBs for primary or secondary prophylaxis of PH-related bleeding before receiving DAA for HCV. Hepatic-venous pressure gradient (HVPG) was measured at baseline, and under chronic therapy with NSBBs before DAA and again after 24-weeks of achieving sustained virological response (SVR) with DAA.
Results: 51 patients were included, 17(33%) on secondary and 34 (67%) on primary prophylaxis. 32(63%) were Child-Pugh class A and 19(37%) class B, 27(53%) were compensated and 24(47%) had previous decompensation of cirrhosis. All were treated with NSBBs. : 30(59%) with propranolol (mean dose: 60 mg/d, IQR: 40–80) and 21 (41%) with carvedilol (mean dose: 18,5 mg/d, IQR: 12.5–25). 26 patients (51%) were hemodynamic responders to NSBBs (HVPG decrease ≥10% from baseline) and had. Baseline characteristics were similar baseline characteristics than non-responders. All patients had SVR. The HVPG-reduction achieved with DAA vs the baseline-HVPG, was greater in responders to NSBBs than in non-responders (20% ± 19% vs 7% ± 19%, P = 0.04). As compared to the HVPG-value under NSBBs, DAA achieved a significant HVPG-decrease in non-responders to NSBBs (from 16.8 ± 3 to 15.4 ± 3 mmHg, P = 0.001) but not in responders (from 15.9 ± 4 to 15.5 ± 4, P = 0.53), reaching a greater relative reduction (12% ± 11% vs 2 ± 22%, P = 0.05).
Conclusion: In patients with HCV-cirrhosis and CSPH receiving chronic prophylaxis with NSBBs, as compared with HVPG-value under NSBBs, DAA therapy has a greater HVPG-lowering effect in hemodynamic non-responders to NSBBs than in responders, although the final HVPG-decrease from baseline-HVPG was greater in hemodynamic responders to NSBBs. This suggests that hemodynamic non-responders to NSBBs may also achieve a benefit from etiological therapy in terms of HVPG-reduction.

SAT118

Improving nutritional care in patients with liver cirrhosis: a quality improvement project

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Background and Aims: The nutrition status of patient with chronic liver disease is known to correlate with disease progression, complications and prognosis. This has resulted in the development of recent guidelines by both EASL and ESPEN on the management of clinical nutrition in liver disease. A liver nutrition care pathway was developed at the University Hospitals of Leicester, NHS Trust to facilitate the delivery of the highlighted recommendations with the aim of improving the quality of nutritional care in patients with cirrhosis. However, the adherence to this pathway has been poor. The aim of this quality improvement project (QIP) is to increase adherence to this pathway in the hepatology unit.
Method: All cirrhotic patients admitted are nutritionally assessed and commenced on the care pathway (see figure 1). Using the 'Plan, Do, Study, Act' (PDSA) QIP methodology, a multidisciplinary team was created to identify ways to improve adherence over a five week period. Three sets of data were prospectively collected on week one (week beginning 30th September 2019), three and five respectively with weeks two and four reserved for interventions. Some of the interventions undertaken included ward staff education, electronic prescribing for nutritional supplements, identification of a 'nurse champion' and promotion via the 'ward newsletter'. Data analysis were focused on adherence to key points including appendices filed, dry weight record, oral nutrition supplementation, food chart commencement and review at day four. Fisher's exact and Student's t-test were used for statistical analysis between week one and week five.
Results: Week 1 (n = 16):- mean age was 59 (SD 12) and 38% (n = 6) were female. Mean Child-Pugh score was 8.6 (SD 2). Number of appendices printed 0 (n = 16). 43.8% (n = 7) had high-energy protein (EP) supplements and 12.5% (n = 2) had carbohydrate (CB) offered. Dry weight estimate was measured in 12.5% (n = 2) of patients and food chart commenced in 75% (n = 12) of patients. Adequate day four food chart (FC) review was not performed in all patients. **Week 5** (n = 16):- mean age was 57 (SD 12) and 56% (n = 9) were female. Mean Child-Pugh score was 11 (SD 2). Percentage of appendices printed had improved to 75% of patients ($p < 0.001$). 87.5% (n = 14) of patients had EP supplements prescribed ($p = 0.023$) and 81.3% (n = 13) had CB offered ($p < 0.001$). There has also been an increase in documentation of dry weight (n = 2 vs n = 7, p = 0.046) and FC review (n = 0 vs n = 10, $p < 0.001$).
Conclusion: This ongoing QIP was successful in improving nutritional care for patients with cirrhosis over a short period. Significant improvement was achieved in appendices filed, dry weight estimate, oral nutrition including EP and CB supplementation and FC review. A key cofounder is the greater severity cirrhotic disease assessed on week five as compared to week one.

SAT119

90-day mortality is lower after as compared to before transjugular intrahepatic portosystemic shunt at the same model for end-stage liver disease score

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Background and Aims: The Model for End-stage Liver Disease (MELD) score has originally been developed to predict 90-day mortality in cirrhotic patients after transjugular intrahepatic portosystemic shunt (TIPS). As the MELD score correlates with the severity of chronic liver disease, it is nowadays employed to stratify patients on a liver transplant waiting list according to urgency. TIPS reduces portal pressure at the cost of hepatic cellular function. It is unclear if the association between MELD score and 90-day mortality remains unaltered after placement of TIPS. MELD may be associated with a different mortality if measured after as compared to before TIPS.
Method: We retrospectively analyzed 179 consecutive patients with cirrhosis that received a TIPS procedure between 2004–2015. MELD scores before TIPS, and 30, 90 and 365 days after TIPS, as well as respective 90-day mortalities were calculated. Gender, age at TIPS insertion, time since TIPS procedure, MELD scores and timing of

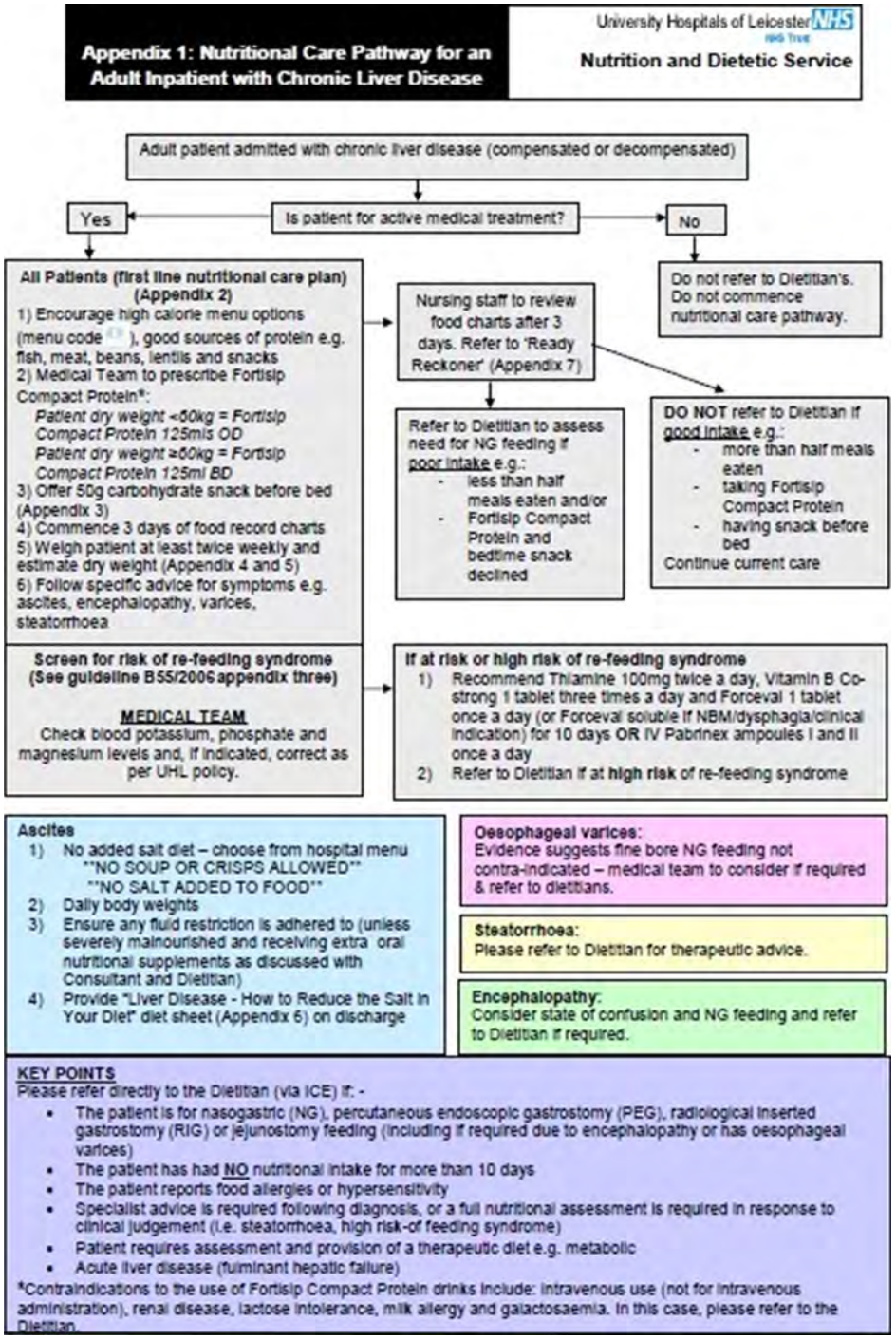
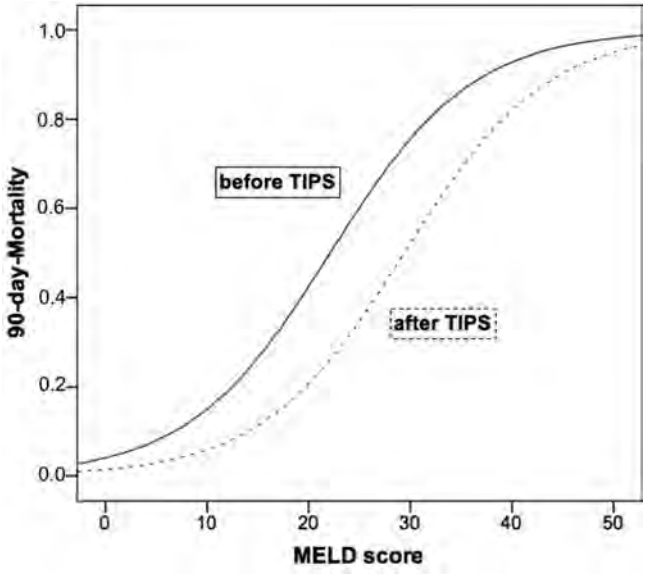


Figure: (abstract: SAT118): Local nutritional care pathway for an adult inpatient with chronic liver disease.

MELD score (before or after TIPS) were inserted as variables in a binary logistic regression with 90-day mortality as an end-point.

Results: Among the study population (n = 179), 69.4% were male, mean age was 60.3 ± 10.6 years and mean MELD score before TIPS was 16.0 ± 6.1. 76.0% underwent TIPS procedure because of ascites, 46.5% because of hemorrhage. In binary logistic regression analysis, only MELD score (p < 0,0001) and timing of MELD score before compared to after TIPS (p = 0,022) were significant predictors of 90-day mortality. Relative risk (95% confidence interval) for mortality per MELD point increase was 1.151 (1.10–1.20), for MELD before TIPS compared to after TIPS it was 0.457 (0.234–0.894). At MELD scores of 10, 20 and 30 mortality rates were 15% versus 6%, 42% versus 21% and 76% versus 52%, respectively, when measured before versus after TIPS insertion. The other variables were not significantly associated with mortality.

Conclusion: Our results suggest that the same MELD scores may be associated with a lower mortality if taken after as compared to before TIPS placement. This may have implications for liver allocation systems, as MELD scores of patients after TIPS may overestimate true waitlist mortality, unintentionally prioritizing these patients for liver transplantation.



SAT120

Long-term prospective study of development of hepatocellular carcinoma in compensated cirrhosis

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Background and Aims: Hepatocellular carcinoma (HCC) is the 5th most frequent incident solid tumor in males and the 2nd for mortality. Main risk factors for HCC development have been mostly identified in retrospective cohorts. With the aim of identifying clinical and biologic risk factors for HCC development, we started in 2013 a prospective study in patients with liver cirrhosis undergoing hepatic venous pressure gradient (HVPG) measurement (ClinicalTrials.gov Identifier: NCT03083002).
Method: 445 consecutive patients with liver cirrhosis (66.5% CP-A, 23.2% CP-B, 10.3% CP-C) undergoing HVPG measurement and transjugular liver biopsy at the Gastroenterology Unit, Modena, were enrolled in this prospective study starting July 2013. Patients were followed up every 6 months with US and blood tests. Those developing HCC in the first 6 months of follow-up were excluded. Data regarding etiology, portal vein, portal vein thrombosis, HVPG, presence and grading of esophageal varices, Child-Pugh and MELD Score, time of development of HCC were collected. Incident cases of HCC were biopsied for pathological and transcriptomic characterization. Independent risk factors for HCC were evaluated by Cox regression analysis.
Results: Median follow up was 40 months. 61 patients died during follow up, 35 developed HCC (M/F 29/6)(incidence 4–5% per year). Preliminary results of analysis of hepatic and circulating biomarkers of angiogenesis, portal hypertension and fibrosis as predictive factors for HCC development indicate marked activation of neoangiogenesis as related with HCC risk. At univariate analysis HVPG>15 (but not HVPG>10 or >20 mmHg), F2/F3 esophageal varices, viral vs. non-viral etiology, and albumin were statistically associated with HCC development (HVPG/F2-F3 varices collinear). In multivariate model with HVPG>15, none of these factors was significantly associated with HCC development while in the model with F2/F3 esophageal varices, presence of the latter was independently linked with HCC development (HR 2.258, 95% CI 1.135–4.494). Albumin only had borderline significance (0.586, CI%.337–1.018).
Conclusion: In this prospective cohort of patients with compensated liver cirrhosis, neither HVPG>10, >15 or >20 mmHg was independently associated with HCC development. Previous data indicating HVPG>10 as a significant risk factor for HCC were likely influenced by the cohort studied, which was free of varices at enrollment. In a cohort of compensated patients with liver cirrhosis not selected for absence of varices, more severe portal hypertension as indicated by F2/F3 varices was the only independent risk factor for HCC development. Presence of F2/F3 varices was related with activation of hepatic neoangiogenesis.

SAT121

First-line empirical antibiotics failed to control bacterial infections resistant to multi drugs in patients hospitalized with cirrhosis

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Background and Aims: Patients with cirrhosis are prone to developing bacterial infection due to immune-dysfunction and repeated hospitalizations. Recent data report a high prevalence of multidrug-resistance organism (MDRO) infection in patients with cirrhosis in Europe and other continents whereas data are limited in China. We aimed to characterize the prevalence, response to first-line empirical antibiotic and survival of MDRO infection in patients hospitalized with cirrhosis.
Method: We prospectively analyzed 155 episodes of infection in 129 consecutive hospitalized patients with cirrhosis in a tertiary center between June, 2016 and July 2018. Data on demographic, clinical, laboratory, microbiology, treatment were collected and analyzed. Treatment response and survival were compared between patients with and without MDRO infection and also between patients with and without accordance to the first-line empirical antibiotics, which was classified according to the Chinese guideline or the EASL guideline for the management of patients with decompensated cirrhosis.
Results: Pneumonia (43.9%), spontaneous bacterial peritonitis (18.7%) and urinary tract infections (7.7%) were the most frequently identified infections. Most of the infections were hospital-associated, including 39.4% of health-care associated and 46.5% of nosocomial infections. 40.6% of the infections were culture-positive, of which 38.8% were caused by MDRO with 65.4% of Enterobacteriaceae bacteria and others. Extended-spectrum beta-lactamase-producing Escherichia coli (38.5%) was the most frequent MDRO followed by Vancomycin-susceptible Enterococcus (15.4%), Carbapenem-resistant Klebsiella (11.5%) and Carbapenem-resistant Acinetobacter baumannii (7.7%). Patients with MDRO infections were closely (all $p < 0.001$) associated with poorer efficacy of first-line empirical antibiotic treatment, higher incidence of acute kidney injury and acute-on-chronic liver failure (ACLF), and lower 28- and 90-day transplant-free mortality comparing to those caused by non-MDRO infections. The accordance of the empirical antibiotic treatment with the national or international guideline did not significantly affect the clinical outcome. However, the failure of first-line empirical antibiotic treatment (sHR, 95%CI: 0.1, 0.02–0.36), presence of ACLF (sHR, 95%CI: 5.1, 2.6–10.0) and sepsis infection (sHR, 95%CI: 4.7, 2.4–9.0) were the most significant independent risk factor of 28-day transplant-free mortality.
Conclusion: MDRO is prevalent with negative impact on prognosis in our cohort from China. Currently recommended first-line empirical treatment by the national and International societies failed to control MDRO infections thereby leading to poorer survival. Specific local antimicrobial strategies need to be established.

SAT122

The SALTYFOOD trial: a randomized, controlled trial of home-delivered low-sodium meals for the management of refractory ascites

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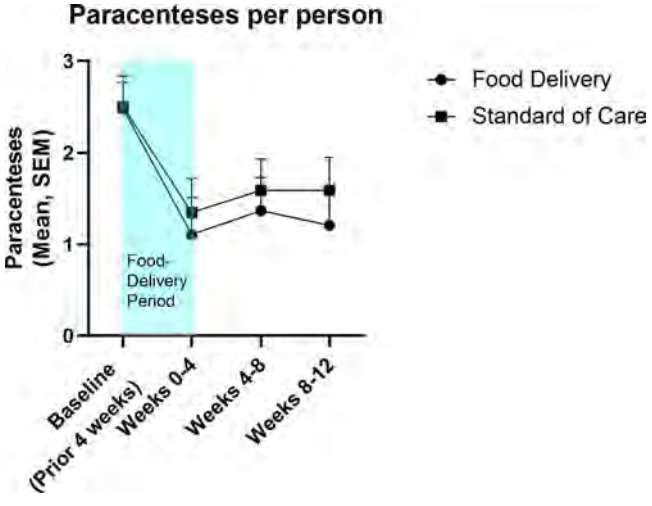
Background and Aims: Refractory ascites is a costly, morbid complication of cirrhosis. Re-accumulation of fluid after paracentesis is associated with risk of hospitalization and infection. Although low-sodium diet is central to the clinical management of ascites, its efficacy is limited by poor adherence. We aimed to determine the impact of home-delivered low-sodium meals on clinical and patient-reported outcomes.
Method: We enrolled 40 persons with cirrhosis and ascites at the time of their outpatient paracentesis or hospitalization with symptomatic ascites in a 1:1 randomized trial of standard-of-care (SOC) (an educational hand-out on low sodium diet) or home-delivered meals with <2000 mg of sodium, >2100 kilocalories, and ≥80 g of protein including a nocturnal protein supplement (Clinicaltrials.gov:NCT03493204). The food intervention took place from weeks 0–4. All patients were followed for 12 weeks with frequent phone assessments. The primary outcome was number of paracenteses performed during weeks 0–12. Baseline and end-of-study assessments included measures of liver function (MELD-Na, albumin), frailty/disability (hand-grip, ADLs, falls), and ascites specific quality of life (ASI-7 scores, range 0–28).
Results: Subjects were aged 54 (47–63), 46% female, 44% diabetic, 44% fully ADL-independent, with MELD-Na 18 (11–23) and albumin 2.7 (2.5–3.3). At baseline, subjects reported a median of 2 (1–3) paracenteses in the prior 4-weeks.
Outcomes: After 12 weeks, patients in the food-arm required fewer paracenteses than those in SOC, 0.34 (0.14–0.54) versus 0.45 (0.25–0.64) per week. Four patients (20%) in the SOC arm died while 2 (10%) and 1 (5%) in the food-arm died and were transplanted. Ascites specific quality of life was improved to a greater degree in the food-arm compared to SOC, by 25% (−11% −61%) versus 13% (−28% −54%). Frailty measures were unchanged.
Feasibility: The intervention was well received though patients with poor dentition or lactose intolerance suggested more meal choices. Adherence to the meal schedule was excellent save for when hospitalizations occurred.



Conclusion: A trial of home-delivered low sodium/high protein meals tailored to the needs of persons with ascites is feasible and potentially effective at reducing the need for therapeutic paracentesis and improving quality of life. Both arms experienced benefits, highlighting the role for improved education and closer monitoring in this challenging condition.

SAT123

The diagnosis of sarcopenia by quadriceps muscle ultrasound in patients with liver cirrhosis

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Background and Aims: A frequent complication in patient with liver cirrhosis is Sarcopenia, that is also associated with a worse prognosis. The diagnosis of sarcopenia is made by Computed Tomography (CT), that allows to calculate the skeletal muscle index (SMI). The quadriceps muscle thickness, measured by ultrasound, would be a bedside, less expensive, faster and easier tool in the detection of sarcopenia in cirrhotic patients. Our study had the aim to evaluate the role of quadriceps muscle thickness pressure index (TPI) in comparison to SMI.
Method: Consecutive cirrhotic patients, who had performed a CT scan within 8 weeks were included. Sarcopenia was evaluated at L3 using Carey et all. cut-offs. The TPI was performed in the middle point on a line connecting the patella with the upper anterior iliac spine. Three measurements with pressure to collapse the muscle were taken. TPI was obtained by the average of these measures normalized for the height.
Results: One-hundred patients were enrolled in the study (mean age 62,9 ± 10,9 years, mean BMI 26,1 ± 4.7 Kg/m², 80% male, 64% with diagnosis of HCC). According to CT imaging, 58% of these patients had a diagnosis of sarcopenia. Sarcopenic patients were older (65 ± 10.8 vs 59 ± 10; $p = 0.05$), with lower BMI (24.3 ± 3.6 vs 28.5 ± 4.9; $p < 0.001$). We found a positive correlation between SMI and TPI ($r = 0.58$; $r^2 = 0.34$; $p < 0.001$). The area under the ROC curve for TPI, considering sarcopenia by SMI the gold standard, was 0.72. The cut-off for the diagnosis of sarcopenia with TPI was 4.85 mm/m^2: the sensitivity was 57%, specificity 80%.
Conclusion: The US assessment of sarcopenia may allow monitoring the patient over time. The results of our study shows that TPI could be an effective index for the assessment of muscle depletion in cirrhotic patients but, although the specificity is high, the sensitivity is rather low. Further study on cirrhotic patient would be necessary to detect better cut-off, especially more specific by gender.

SAT124

Interest of echocardiography in the management of acute kidney injury in cirrhotic patients with ascites. Results of the prospective pilot cirren study

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Background and Aims: Acute kidney injury (AKI) is a severe complication of decompensated cirrhosis. Haemodynamic changes as the presence of left ventricular diastolic dysfunction may predict the risk of hepatorenal syndrome (HRS) and mortality for patients with ascites. Haemodynamic characteristics of cirrhotic patients with concomitant AKI have not been reported yet. We aimed to describe haemodynamic changes in a cohort of cirrhotic patients with non-organic AKI.
Method: We prospectively recruited 26 cirrhotic patients with ascites and non-organic AKI (as defined by the International Club of Ascites). Echocardiography was performed at the time of diagnosis before plasma volume expansion. Diagnosis of renal injury (HRS or

functional AKI) was retrospectively determined according to response to plasma volume expansion. A control cohort of 25 non-AKI cirrhotic patients with ascites was used to compare haemodynamic changes in non-organic AKI.

Results: AKI and control cohorts were similar regarding CHILD-PUGH score, bilirubin, albumin and INR levels. The AKI patients displayed a median creatinine level of 134 µmol/L and showed significantly lower serum sodium levels (median 132 vs 136 mmol/L for AKI and controls, respectively; $p = 0.01$). Left ventricular ejection fraction (LVEF) was significantly decreased in AKI patients compared to controls (60% vs 68%; $p = 0.006$). The median lateral e' velocity and e/e' ratio were 9.5 cm/s versus 11 cm/s and 6.9 vs 7.5 respectively in AKI and control groups ($p > 0.05$). No difference of septal e' velocity, e/a ratio, tricuspid velocity or left atrial surface was found between groups. Although no patients exhibited clinical signs of left heart failure, increased left ventricular filling pressure (LVFP) before plasma volume expansion was found for 1 AKI patient. In the AKI group, serum sodium level was lower at inclusion for 9 HRS patients compared to others (130 vs 133 mmol/L respectively; $p = 0.03$). No difference according to creatinine levels or echocardiography characteristics was reported between HRS and other AKI patients.

Conclusion: Serum sodium level and LVEF were significantly altered in AKI cohort compared to control cirrhotic patients. Echocardiography may reveal patients with high LVFP despite normal examination, and may be of interest to manage plasma volume expansion. Further studies are needed to explore the relevance of echocardiography and serum sodium levels for the management of AKI in cirrhotic patients.

SAT126

Head to head comparison of liver stiffness measurement using transient elastography, 2D-shear wave elastography and magnetic resonance elastography for non-invasive evaluation of clinical significant portal hypertension

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Background and Aims: Portal hypertension contributes to the main complications of cirrhosis and to patients' mortality. Several liver elastography-based approaches, namely transient elastography (TE), 2-dimensional shear wave elastography (2DSWE-SSI) and magnetic resonance elastography (MRE), have been proposed for the non-invasive assessment of portal hypertension. However, the ability of these approaches to estimate clinically significant portal hypertension (CSPH - hepatic venous pressure gradient (HVPG) ≥10 mm Hg) has never been compared head to head. The aim of this work was to compare technical success rate and diagnostic performance of TE, 2DSWE-SSI and MRE for detection of CSPH in patients with compensated cirrhosis.

Method: This monocentric prospective study included patients with biopsy-proven cirrhosis, without any history of liver decompensation, who underwent liver TE, 2DSWE-SSI, MRE and HVPG measurements within less than 30 days. Technical success rate was defined for TE according to EASL guidelines, for 2DSWE-SSI as temporal stability of the selected area for ≥3 seconds, homogenous color in the region of interest and measurement region of ≥10 mm, and for MRE as any value obtained. Ability of estimating HVPG and identifying patients with HVPG ≥10 mm Hg was compared between TE, 2DSWE-SSI and MRE using area under ROC curve (AUROCs).

Results: We included 44 patients: 32 men; median age 58 years; median BMI 26 kg/m^2; median MELD 9; cirrhosis related to alcohol (n = 12), HCV (n = 19), HBV (n = 7), NASH (n = 3), other (n = 3); 35 with hepatocellular carcinoma; 26 with CSPH. Technical success rate was

Techniques	AUROC	Cut-off values obtained using Youden index*	Se (%)	Sp (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)
LS using TE (kPa)	0.813	20.3	81	73	81	73	78
LS using 2DSWE-SSI (kPa)	0.810	17.1	76	80	80	69	75
Gd (kPa)	0.797	5.3	67	93	93	67	77
Gl (kPa)	0.778	2.7	67	93	93	67	77
Gabs (kPa)	0.794	6.0	71	87	88	68	77

Abbreviations: LS, liver stiffness; kPa, kilopascals; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value. Gd, storage modulus; Gl, loss modulus, Gabs, shear modulus

Figure: (abstract: SAT126): Diagnostic performance of TE, 2DSWE-SSI, and MRE for detecting CSPH in 36 patients with technical success.

higher with liver MRE (100%), than with liver TE (89%; p = 0.024) or liver 2DSWE-SSI (93%; p = 0.075). HVPG correlated with liver TE (r = 0.692; p < 0.0001), 2DSWE-SSI (r = 0.623; p < 0.0001), and liver MRE parameters [storage modulus (Gd), r = 0.522, p = 0.001; loss modulus (Gl) r = 0.540, p = 0.0007; shear modulus (Gabs) r = 0.529, p = 0.0009)]. As compared with patients with HVPG <10 mm Hg, patients with CSPH had higher liver stiffness by TE (17 vs. 32 kPa; p = 0.01), 2DSWE-SSI (14 vs. 20 kPa; p = 0.008) or MRE (Gd 3.8 vs. 5.9 kPa, p = 0.01; Gl 1.9 vs. 3.2 kPa, p = 0.005; Gabs 4.5 vs. 7.0 kPa; p = 0.008). AUROCs of TE, 2DSWE-SSI, and liver MRE parameters ranged from 0.81 to 0.78 and did not significantly differ between the 3 methods, when including patients in whom the three methods were successfully performed (Table).

Conclusion: In patients without any history of cirrhosis decompensation, liver TE, 2DSWE-SSI and MRE correlated well with HVPG and had similar performance for detecting CSPH.

SAT127

A hypercoagulable state does not play a major role in the development of portal vein thrombosis in patients with cirrhosis

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Background and Aims: Patients with cirrhosis (CH) are at increased risk of developing portal vein thrombosis (PVT). Liver disease is associated with changes in the pro- and anti- coagulant factors conferring an instable homeostatic rebalance that is thought to enhance thrombotic risk although studies specifically addressing the impact of the hemostatic status on PVT development are lacking. Other factors such us severity of portal hypertension (esophageal varices, portal blood velocity (PBV) <15 cm/s), severity of liver disease, etiology of liver disease, obesity and use of non-selective BB have been suggested to facilitate PVT.

The aim of the current study is to evaluate the role of the hemostatic status on peripheral blood on PVT development.

Method: Consecutive patients with CH submitted to US-Doppler HCC screening every 6 months were included and prospectively followed-up (Dec 2010–April 2013). Only patients without PVT, HCC and not taking anticoagulants were included. Baseline clinical, laboratory data and PBV were collected. Additionally, baseline peripheral blood samples were used for a comprehensive evaluation of plasma levels of hemostatic proteins, markers of inflammation, neutrophil extracellular traps, functional tests of coagulation, clot stability and fibrinolysis.

Results: Patients were followed-up every 6 months by US to identify PVT development until Feb 2019 or until liver transplantation, death, TIPS placement or initiation of anticoagulation for any reason. 310 patients with CH were included. 59% were male, mean age was 59 ± 11 years. The main causes of cirrhosis were HCV (55.8%) and alcohol (28%); 20% of patients were obese; 72% of patients were Child-Pugh A, 22% B and 6% Child-Pugh C. Medium/large varices were present in 41% patients, 17% had previous variceal hemorrhage and 42% had ascites. 23 patients (7.9%) developed PVT (21 partial, 2 complete) during a mean follow-up of 48 ± 27months.

PVT was more common in patients with severe liver failure, taking NSBB, with EV, low PBV and alterations in hemostatic parameters. However, when Cox regression adjusted for variables assessing the severity of cirrhosis, of portal hypertension, different alteration in hemostatic parameters and use of NSBB was performed, the only variables independently associated with PVT were a baseline PBV <15 cm/sec, low albumin and low Factor X levels.

Conclusion: Based on our results, hypercoagulability does not play a major role in PVT development. Liver failure and reduction of PBV are major risk factors for PVT development.

SAT128

Comparison of the diagnostic quality of aspiration and core biopsy needles for transjugular liver biopsy

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Background and Aims: Liver biopsy remains essential for the diagnostic work-up of patients with liver disease. Here we comprehensively evaluated aspiration vs. core biopsy needles for transjugular liver biopsy (TJLB) in patients undergoing hepatic venous pressure gradient (HVPG) measurements.
Method: All patients undergoing TJLB between 01/2017 and 12/2018 were included. Liver biopsy were performed according to a standardized procedure and specimens were systematically evaluated for quantitative and qualitative criteria such as number of portal tracts (PT), sample length and fragmentation. Quality parameters of liver biopsy specimens obtained by aspiration needle vs. core biopsy needle were compared.

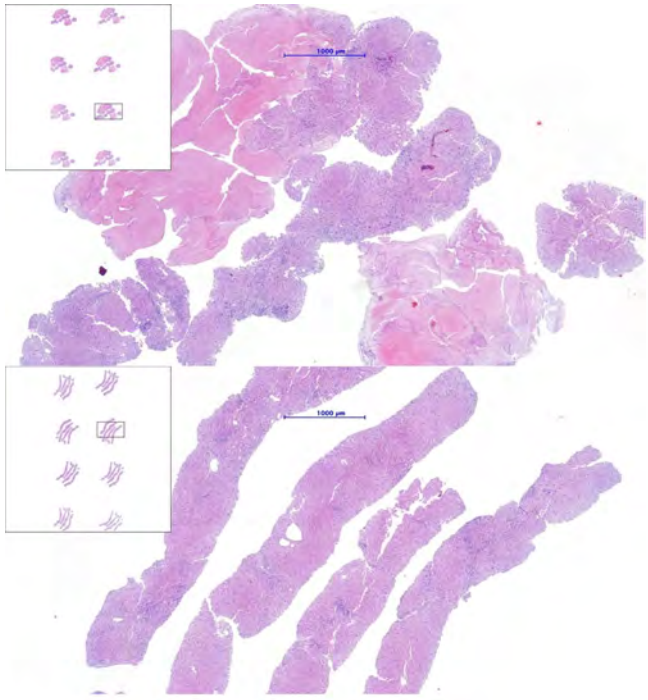

Figure: Representative liver biopsy specimens with an aspiration needle (above) and core biopsy needle (below).

Results: 84 patients with a median MELD of 14 (IQR: 9–21) and a median HVPG of 12 (IQR: 5–19)mmHg were included. 56 patients (66.7%) had decompensated liver disease and 68 patients (81.0%) advanced fibrosis/cirrhosis (F3/4) on histology. In direct comparison of paired TJLB specimens, core biopsy samples were significantly longer (median 12 [IQR: 10–17] vs. 9 [IQR: 6–15]mm, p = 0.012), tended to contain more PT (median 8 [IQR: 5–18] vs. 6 [IQR: 2–11], p = 0.064) and were less fragmented (p < 0.001), which resulted in better confidence for liver fibrosis assessment (p = 0.035). However, a superior quality in terms of less fragmentation of core biopsy specimens (p < 0.05) was only confirmed in patients with HVPG ≥10 mmHg or LSM >40 kPa. In contrast, the aspiration needle provided significantly longer samples in patients with HVPG <10 mmHg (median 21 [IQR: 13–30] vs. 12 [IQR: 9–16]mm, p = 0.007) or with LSM <20 kPa (median 21 [IQR: 13–34] vs. 11 [IQR: 9–20]mm, p = 0.025). No major biopsy-related complications occurred.
Conclusion: In patients with HVPG ≥10 mmHg or LSM >40 kPa TJLB should be performed by using core biopsy needles, while the aspiration needle provides high quality liver biopsy specimens in patients with HVPG <10 mmHg or LSM <20 kPa.

SAT129

Spleen stiffness-based models can predict presence of esophageal varices in patients with compensated liver cirrhosis stratified by liver disease etiology

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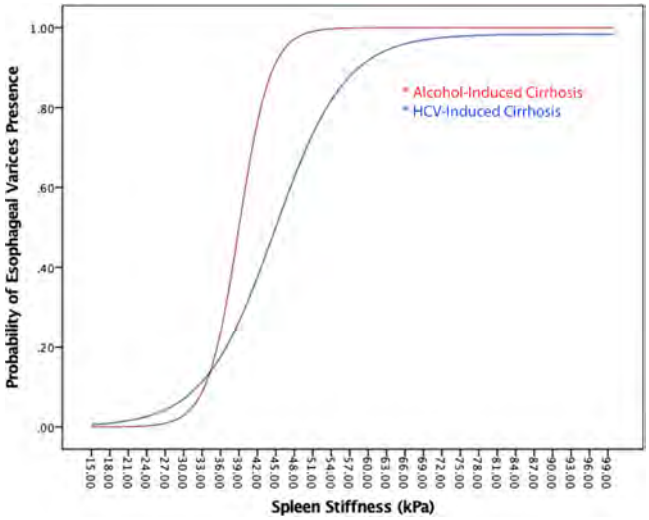
Background and Aims: Recent findings showed that even small-size esophageal varices (EVs) have to be considered as a disease stage more prone to hepatic decompensation. We want to evaluate the predictive capability of spleen stiffness (SS) as a non-invasive surrogate to appropriate EVs screening.
Method: We measured spleen stiffness (SS) using point-Shear Wave Elastography with Philips Affiniti 70 system in 219 patients with compensated liver cirrhosis, whose etiology was HCV in 96 patients and alcohol abuse in 123 patients. In total, 97 patients had EVs at screening endoscopy. The association between varices (discrete; 0 = no, 1 = yes) and LS and SS was evaluated using logistic regression. According to statistical results we created a SS-based models in which the linear predictor (LP) was employed to calculate the probability of EVs using the following formula: {1-[1/(1+e^(LP))]}.



Results: Patients with HCV-induced cirrhosis had a LP of −6.813 + 0.164*SS. The model had the following discriminative and calibration metrics: AIC = 142, BIC = 147, AUROC = 0.92, Pseudo-R2 (Nagelkerke) = 0.6, Hosmer-Lemeshow (p-value) = 0.085. Instead, the LP in patients with alcohol-induced cirrhosis was equivalent to −15.208 + 0.39*SS. This model showed AIC = 163.5, BIC = 166, AUROC = 0.97,

Pseudo-R2 (Nagelkerke) = 0.804, Hosmer-Lemeshow (p-value) = 0.509. The two probability curves (figure) showed a different behavior, with a more rapid increase of the slope of the alcoholic's curve if compared to patients with viral hepatitis.
Conclusion: It was possible to create a probability model according to SS-values that could decide to spare endoscopic screening in low-risk patients (for any grade of EVs). Having a given probability instead of a single number to rule-in or rule-out a specific event is indeed more helpful and could support the clinician in the decision of performing an invasive test if the probability is high. Cut-off values, even if they are chosen to be the most sensitive or specific, are always subjects to false-positives and false negatives; and, sometimes, even with low LS and SS, the clinical presentation may require more invasive tests, making cut-offs pointless. In conclusion, the results of this study further emphasize the potential clinical relevance of SS measurement by pSWE elastography in the clinical workup of cirrhotic patients.

SAT130
Ammonia is an independent biomarker of poor outcomes in patients with advanced cirrhosis
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Background and Aims: The role of ammonia as a prognostic biomarker in patients with cirrhosis remains unclear. The aim of this study was to determine whether ammonia levels in patients with advanced cirrhosis awaiting liver transplantation influence major waiting list outcomes.
Method: Retrospective observational study of sequential cirrhotic adult patients listed for liver transplantation between January 2015 and December 2018. All patients had an arterial ammonia measured at the time of assessment for transplant. All patients were closely followed up until death or transplantation. The main outcomes were hospital admissions, infection, organ failures and mortality. Multiple logistic regression was performed using independent variables that were significantly associated with wait-list outcomes on univariate analysis.
Results: 300 patients were included (mean age: 54 ± 10 years). Mean follow-up time was 723 days. 266 (88.7%) patients were transplanted, 15 (5.0%) were de-listed for being too sick for transplant or following clinical improvement, 14 (4.7%) died on the list and 5 (1.6%) were still active on list. 97 patients (32.3%) had at least one hospitalization while on the waiting list. On multiple logistic regression arterial ammonia was independently associated with hospitalization, infection and ACLF. Ammonia level was associated with mortality ($p = 0.001$) in patients listed for liver transplantation and the development of post-transplant complications ($p < 0.001$) (Table 1). Arterial ammonia was superior to standard organ severity scores at predicting outcomes of infection (AUC 0.79), hospitalization (AUC 0.81), ACLF (AUC 0.80) and mortality (AUC 0.73) in patients listed for liver transplantation.
Conclusion: Arterial ammonia at the time of listing for liver transplantation was an independent predictor of hospitalization, ACLF, infection and mortality. These data suggest that blood ammonia may be an important determinant of wait-list survival.

SAT131
Survival outcomes of SBP, BA and CNNA in a large Scottish cohort
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Background and Aims: Spontaneous bacterial peritonitis (SBP) has significant mortality rate even if treated. Diagnosis is based on the white cell (WCC) or neutrophil count and a positive culture of pathogens in the ascitic sample. The greatest sensitivity for the diagnosis is reached with a cut-off neutrophil count of 250/mm^3; where a differential is not available a WCC of 500 cells/mm^3 is used. When the sample doesn't meet the criteria, two other conditions are described: bacteriascites (BA) – the presence of a cultured pathogen without the WCC elevation, and culture negative neutrophilic ascites (CNNA) – the lack of a pathogen culture with the WCC elevation. Prognosis and guidelines for treatment of these conditions are less clear. The aim of this study was to characterise a large cohort of patients with these conditions and analyse any differences in their survival.
Method: Microbiology laboratory databases within Greater Glasgow Health Board were searched for all ascitic fluid samples from January 2014 to December 2017. Samples from non-cirrhotic ascites were excluded. Episodes were allocated a diagnosis of SBP, BA, CNNA at a WCC cut-off of 250 and 500, and survival (days from the ascitic tap to death) was analysed. A small sample of negative cases were included for comparison.
Results: A total of 2050 episodes were identified. 180 episodes were analysed (including negative). When a cut-off value of 500 WCC was used, there were 40 episodes of SBP, 42 of BA, 52 of CNNA and 46 negatives. When the 250 WCC cut-off was applied, the numbers were: SBP = 47, BA = 35, CNNA = 82, negatives = 16.
78 died during admission (43%) and 105 died within 90 days of the tap (58%). The average time to death was 125 days (median = 20).

Dependent Variable	Significant independent variables	Exp(B); OR (95% CI)	p value	AUC
Infection	Ammonia	1.03 (1.02-1.03)	p < 0.001	0.79
	INR	2.48 (1.54-4.92)	p = 0.001	0.68
Hospitalization	Ammonia	1.04 (1.03-1.06)	p < 0.001	0.81
	UKELD	1.09 (1.00-1.19)	p = 0.040	0.64
ACLF	Ammonia	1.03 (1.02-1.05)	p < 0.001	0.79
	MELD	1.14 (1.07-1.22)	p < 0.001	0.70
Post-operative complications	Ammonia	1.01 (1.01-1.02)	p = 0.002	0.69
	Albumin	0.92 (0.89-0.96)	p < 0.001	0.66
Mortality	Ammonia	1.02 (1.01-1.03)	p = 0.001	0.73
	MELD	1.13 (1.05-1.22)	p = 0.001	0.70

Figure: (abstract: SAT130)

There was a significant difference in survival at the 500 WCC cut-off (except BA vs CNNA). Survival difference in the 250 WCC cut-off groups did not uniformly reach statistical significance. In particular, the difference in BA and SBP was not significant.

		SBP	BA	CNNA	NEG
median survival (days)	cut-off 500	15	89*	547⁺	726⁺
	cut-off 250	15	90	53.5⁺	726.5⁺

*p<0.05 or ⁺p<0.01 when compared with SBP.

Conclusion: SBP is a devastating diagnosis with high mortality and short prognosis. The non-significant survival difference between SBP and BA at the 250 cut-off suggests that BA has equally poor outcomes and warrants as robust investigations and treatment as SBP. Stronger significance values were reached with the 500 cut-off. Accurate diagnosis of SBP, BA and CNNA provides the clinician and the patient with an idea of prognosis.

SAT132

Risk stratification and the effects of early tips among patients with Child-Pugh B cirrhosis and acute variceal bleeding

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Background and Aims: Whether early transjugular intrahepatic portosystemic shunt (TIPS) should be used in patients with Child-

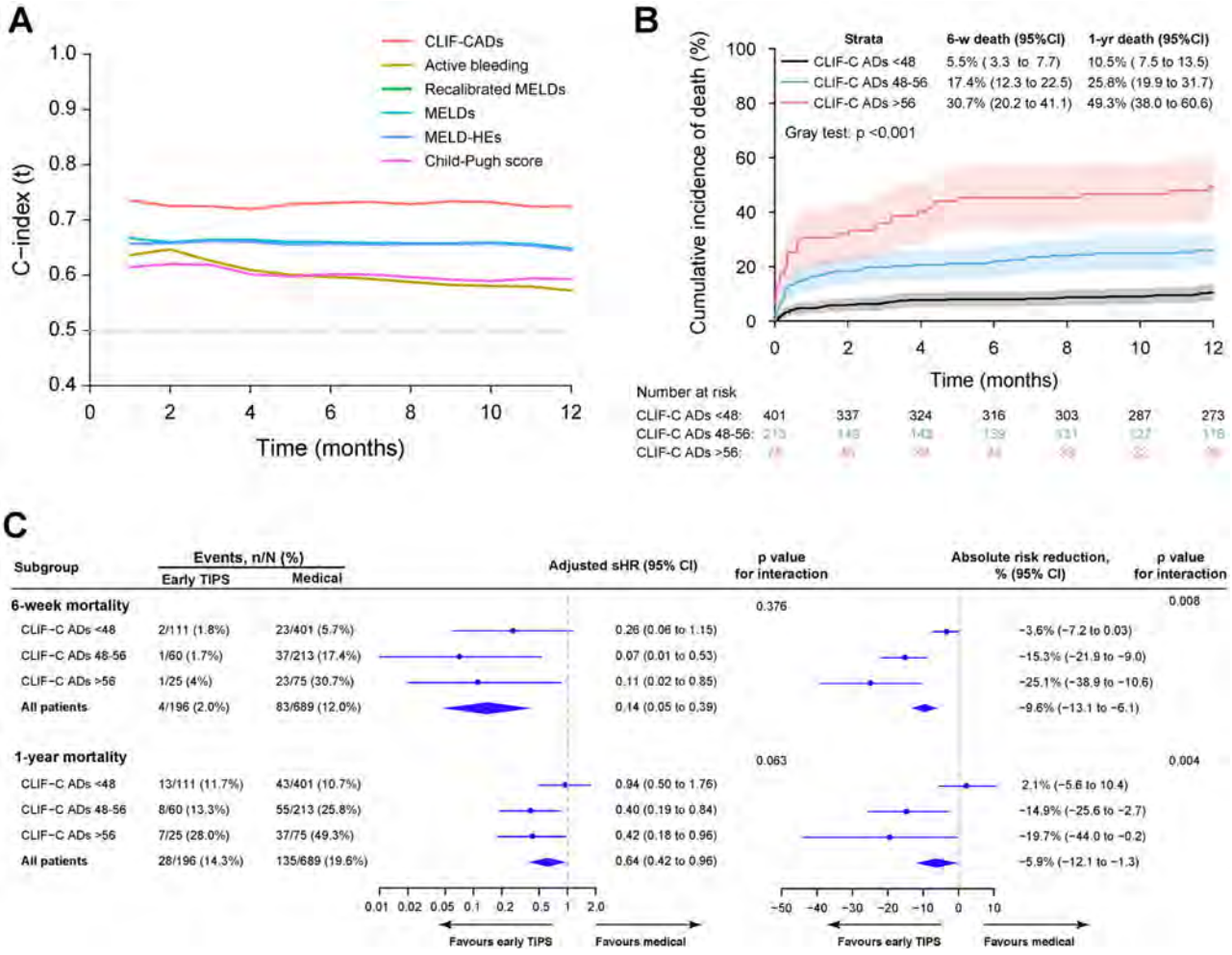

Figure: (abstract: SAT132)

Pugh B cirrhosis and acute variceal bleeding (AVB) remains an open issue. This study aimed to test the hypothesis that risk stratification using CLIF Consortium Acute Decompensation score (CLIF-C ADs) may be useful to identify a subgroup at high risk of mortality who have the greatest benefit from early TIPS in patients with Child-Pugh B cirrhosis and AVB. This study also aimed to assess the prognostic value of active bleeding and whether it modifies the effect of early TIPS.

Method: We analysed the pooled individual data from two published studies of 885 patients with Child-Pugh B cirrhosis and AVB who received early TIPS (early TIPS group, n = 196) or standard treatment (medial group, n = 689) between 2010 and 2017 in China. We compared the performance (discrimination and calibration) of CLIF-C ADs with active bleeding and other prognostic models. The Fine and Gray competing risk regression model was used to compare the outcomes between groups that were stratified based on CLIF-C ADs or active bleeding after adjusting for liver disease severity and other potential confounders.

Results: Early TIPS group had lower mortality than medial group (13.8%% vs 19.4% at 1 year, adjust sHR: 0.64, 95%CI 0.43 to 0.97). When applied to patients receiving standard treatment, the CLIF-C ADs showed satisfactory calibration (Hosmer-Lemeshow test, p = 0.268). The C-index of CLIF-C ADs for 6-week and 1-year death (0.708, and 0.707) were significantly better than those corresponding to active bleeding at endoscopy (0.645 [p < 0.001] and 0.570 [p < 0.001]) and other prognostic models (Figure A). With X-tile software to identify the optimal cutoff value, patients in medical group were categorized as low-risk (CLIF-C ADs <48, n = 401), intermediate-risk (CLIF-C ADs 48–56, n = 213) and high-risk (CLIF-C ADs >56, n = 75), with a 5.5%, 17.4% and 30.7% risk of 6-week death and a 10.5%, 25.8% and 49.3% risk of 1-year death, respectively (Figure B). The absolute mortality reductions with early TIPS were more pronounced in high-risk categories (Figure C). Furthermore, after adjusting for liver disease severity and other potential confounders, a survival benefit was observed in intermediate-risk and high-risk but not in low-risk patients (Figure C). Active bleeding at endoscopy was associated with increased risk of death (sHR 1.84, 95%CI: 1.28 to 2.55; p < 0.001) in medical group. A survival benefit associated with early TIPS was observed in those with active bleeding but not those without active bleeding.

Conclusion: In patients with Child-Pugh B cirrhosis and AVB, risk stratification using the CLIF-C AD score identifies an intermediate-risk and high-risk subset that derive greatest benefit from early TIPS. Active bleeding at endoscopy had prognostic value and could modify the effect of early TIPS.

SAT133

Risk factors for sarcopenia and its impacts on clinical outcome in patients with liver cirrhosis

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Background and Aims: Patients with chronic liver disease are at high risk for sarcopenia, which had been reported to affect up to 70% of patients with advanced liver disease. Our research is aimed to study the incidence of sarcopenia in patients with liver cirrhosis, and explore its risk factors and impact on the clinical outcomes.

Method: A total of 199 inpatients with liver cirrhosis were included in the study. Nutritional risk was assessed by NRS-2002, anthropometric and laboratory parameters were measured. Appendicular skeletal muscle mass index (ASMI) was calculated according the results of body composition analysis. The patients were divided into sarcopenia and non-sarcopenia groups according to the cutoff value of ASMI 7.0 kg/m^2 for male and 7.0 kg/m^2 for female to find the risk factors for sarcopenia. Then the survival and complications of the two groups were compared after following up for 48 years. According to different data, statistical analysis was done using *t*-test, *Chi-square* test and binary logistic regression.

Results: The incidence of sarcopenia was 36.7% in patients with cirrhosis. It was higher in patients with hepatic coma, which was 62.5%, followed by the patients with abdominal/pleural effusion 37.6%. The incidence of sarcopenia in those with nutritional risk was significantly higher than that in those without nutritional risk ($P < 0.05$). However, even in those without nutritional risk, 14.8% of the patients had sarcopenia. BMI, AMC and BCM in the sarcopenia group were lower than those in the non-sarcopenia group ($P < 0.05$), and ECW/TBW was higher than those in the non-sarcopenia group ($P < 0.05$). Multivariate analysis showed that age, sex, BMI and hepatic coma were the main influencing factors of liver cirrhosis with sarcopenia ($P < 0.05$). The mortality rate, incidence of recurrent abdominal/pleural effusion, hepatic coma and infection in sarcopenia group was significantly higher than that in non-sarcopenia group ($P < 0.05$).

Conclusion: Sarcopenia is part of the manifestations of malnutrition in patients with liver cirrhosis, which has adverse effects on clinical outcomes including survival, development of other complications. The older patient, especially the male one, with the lower BMI and hepatic coma may have higher risk for sarcopenia.

SAT134

The burden of cirrhosis on the Canadian healthcare system: a comparison between alcoholic and non-alcoholic cirrhosis patients

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Background and Aims: Recent studies have indicated an increasing burden of cirrhosis in different health care systems. However, the burden of alcoholic vs. nonalcoholic cirrhosis varies worldwide. Therefore, we evaluated the epidemiology of cirrhosis in a Canadian province, and describe the health care utilization patterns of alcoholic vs. nonalcoholic cirrhosis patients.

Method: We used a validated coding algorithm to identify cirrhosis patients in the province of Alberta, Canada (population ~4.4 million) from 2008–2018. We classified cirrhosis patients according to etiology (alcoholic vs. nonalcoholic) using the international clinical classification (ICD), versions 9 and 10. Causes of nonalcoholic cirrhosis included viral, nonalcoholic fatty liver and autoimmune chronic liver diseases. Multiple sources of data including inpatient, ambulatory, emergency room visits, and physician billing were linked. Liver-related hospitalizations or emergency department (ED) visits were identified if the primary code was a cirrhosis-related complication including variceal bleeding, ascites, hepatic encephalopathy, hepatocellular carcinoma and spontaneous bacterial peritonitis.

Results: The overall sex and age adjusted prevalence rate of cirrhosis in Alberta was 68.8 per 10,000 person, while the adjusted incidence rate was 11.2 per 10,000 person. Adjusted incidence and prevalence rates for nonalcoholic cirrhosis were higher than those for alcoholic cirrhosis (Incidence rates 8.6 vs. 2.6 per 10,000 person; Prevalence rates 48.8 vs. 20.0 per 10,000 person). The majority of cirrhosis patients were men (56%), with a median age of 61 years (IQR: 56–64). In our cohort, 31.2% of patients (n = 8,632) had alcoholic cirrhosis. Approximately 38.6% of the cirrhosis patients were hospitalized for cirrhosis-related complications within 1 year after diagnosis, with an estimated median hospitalization cost of $14,133 CAD. The median hospitalization length of stay was 5 days (IQR: 1–19). Liver-related

hospitalizations accounted for 59.8% of all hospitalizations, while liver-related ED visits represented 33.4% of all ED visits. Overall 5-year liver-related hospitalization rates for alcoholic cirrhosis were higher than for nonalcoholic cirrhosis (68.5% vs. 42.0%, p < 0.001). Similarly, 5-year liver-related ED visits were higher among alcoholic than non-alcoholic cirrhosis patients (28.0% vs. 8.1%, p < 0.001).
Conclusion: In our large Canadian population-based study, non-alcoholic cirrhosis represented two thirds of all cirrhosis patients. However, patients with alcoholic cirrhosis were more likely to visit an ED and be hospitalized for liver-related complications. This data suggests that outpatient resources should be focused on patients with alcoholic cirrhosis to improve acute health care resource utilization.

SAT135

Developed and validated a prognostic nomogram incorporating body compositions for long-term mortality in cirrhosis: a sex-stratified analysis

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Background and Aims: Alterations in body composition (BC) as abnormal muscle quantity/quality and adiposity are related to poor outcomes and presence of complications in cirrhosis. However, no predictive tools combining all these anthropometric parameters are applicable in the clinical setting. We aimed to clarify the potential utility of BCs and develop a nomogram incorporating any independent factor for prognosticating long-term mortality in cirrhosis.
Method: A total of 414 cirrhotic patients were randomized into primary (N = 274) and validation (N = 140) cohorts. X-tile was performed to identify optimal cutpoint for stratifying subjects with distinct outcomes. Multivariate Cox regression was performed, and nomogram model incorporating BCs were generated. The utility of developed models were evaluated by Harrell's concordance index (C-index), calibration curve and decision curve analysis.
Results: Stratifying by X-tile derived cutpoints, low SMI (myopenia), high IMAC (myosteatosis) and high VSR (adiposity) were independently associated with 3-year mortality by Cox regression analysis. A sex-stratified nomogram incorporating anthropometric indices and clinical factors resulted in moderate discriminative accuracy, with a C-index of 0.787 (95%CI: 0.736–0.838) and 0.789 (95%CI: 0.727–0.851) in male and female, respectively. The calibration curve showed predictive survival corresponding optimally with the actual outcomes. Our models were feasible in clinical settings based on decision curve analysis. Similar results were observed in the validation cohort. Additionally, participants could be classified into three distinct risk groups (low, medium and high) by the nomogram.
Conclusion: Our proposed nomogram embedding BCs rendered an individualized predictive tool for long-term mortality in cirrhosis.

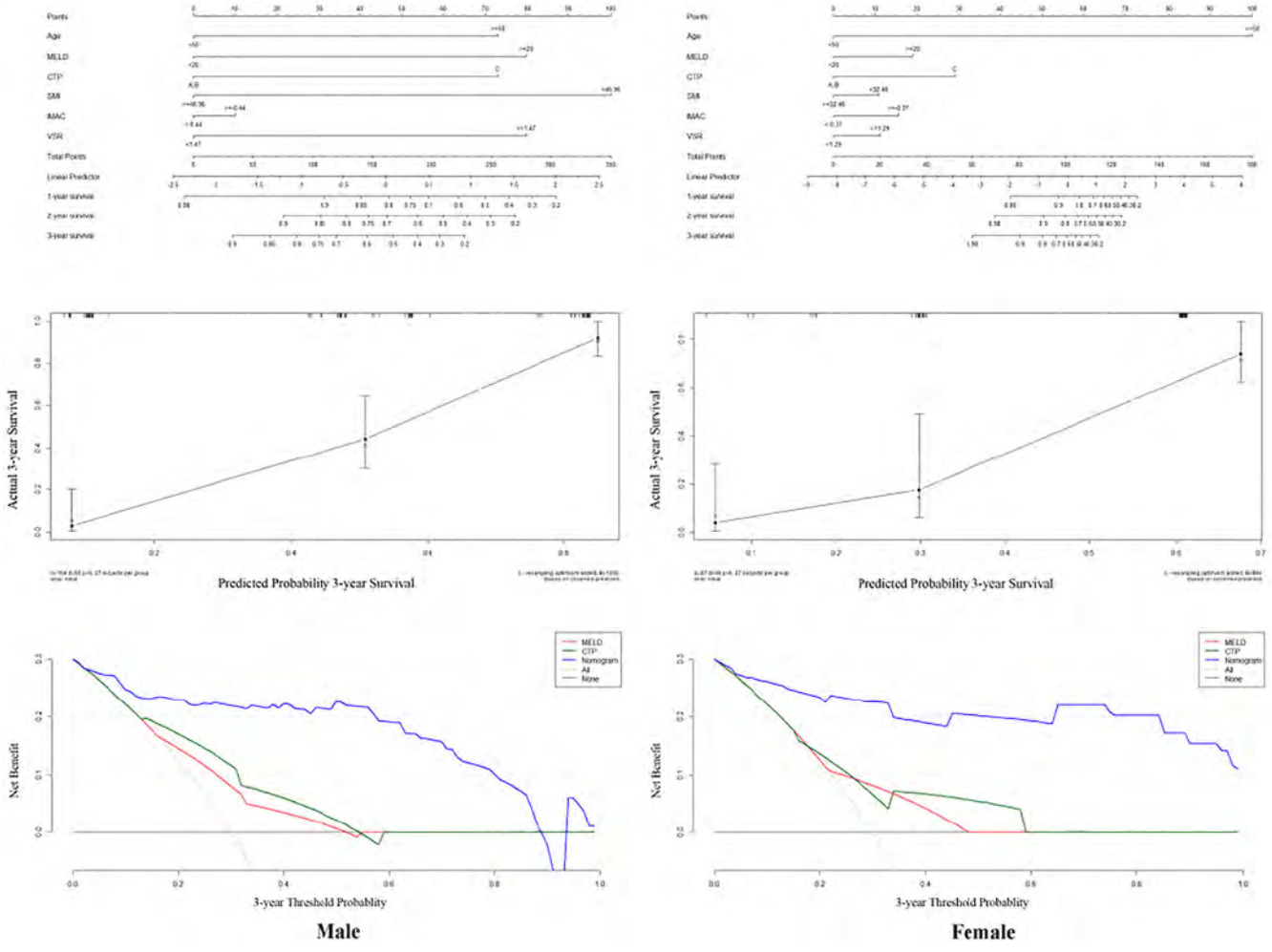

Figure: (abstract: SAT135)

SAT136

Collagen type XVIII is associated with platelet count and meld score in patients with trans-jugular intrahepatic portosystemic shunt

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Background and Aims: Increased turnover of extracellular matrix (ECM) proteins is a hallmark of fibrosis. Changes in basement membrane (BM) remodeling during fibrosis is suggested to play a reparative role as this part of the ECM is important for cell attachment and regeneration. Collagen type XVIII (COLXVIII) is attached to the BM, where it is important for both thickness and stiffness and has been shown to be crucial for hepatocyte survival. COLXVIII is best known for the signaling fragment Endostatin, a potent anti-angiogenic and anti-fibrotic molecule. However, attention is now also directed towards the many biological functions of the tree isoforms (short, medium and long) of COLXVIII. The short and long isoforms together with Endostatin was measured serologically by the ELISA assays COL-18N, PRO-C18L and Endostatin respectively. In a healthy liver, the long isoform of COLXVIII, characterized by a prolonged N-terminal, has been found to be the most abundant isoform whereas the abundance of the short isoform increases in the liver with fibrosis. Here the short isoform of COLXVIII (COL18-N) is investigated as a biomarker of disease in patients with trans-jugular intrahepatic portosystemic shunt (TIPS).
Method: Plasma samples of 110 patients with decompensated liver cirrhosis were taken from portal and hepatic veins at time of TIPS insertion and two weeks later at an invasive TIPS control. Circulating levels of COL18-N before and after TIPS was assessed in plasma using specific monoclonal ELISA and analyzed by Mann-Whitney t-test. Correlation to MELD score and platelet count were investigated by Spearman correlation.
Results: Levels of COL18-N in both the portal and hepatic veins were significantly increased after TIPS insertion ($p > 0.01$ and $p > 0.05$, respectively). MELD score was in addition found to share a negative correlation with COL18-N ($r = -0.23$), while the platelet count and COL18-N were positively correlated ($r = 0.26$).
Conclusion: We show that BM turnover is increased after TIPS and that patients, thus initiating a reparative process after TIPS. In addition, the negative correlation to MELD indicates that patients with high COL18-N levels may have better prognosis compared to patients with low COL18-N. This study shows the potential of COL18-N in assessing fibrosis status in patients after TIPS. Profiling of COLXVIII isoforms may improve non-invasive monitoring of liver fibrosis.

SAT137

Terlipressin vs noradrenaline for the treatment of hepatorenal syndrome in patients with acute-on-chronic liver failure: a 5-year retrospective analysis

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Background and Aims: Hepatorenal syndrome (HRS) is a type of acute kidney injury (AKI) that develops in cirrhotic patients. Most patients with HRS-AKI have acute on chronic liver failure (ACLF). Response to vasopressor treatment and predictive factors of mortality in HRS-AKI patients with ACLF are still unclear.
Method: A retrospective analysis of cirrhotic patients admitted in our intensive care unit from January 2014 to July 2019 was performed. Patients with ACLF and HRS-AKI were treated with albumin plus terlipressin (T) or plus noradrenalin (NA). Patients were censored at the time of death, liver transplantation or end of follow-up.
Results: Among 128 consecutive ACLF patients, 37 were diagnosed as HRS-AKI. No significant differences were observed in demographic, clinical and laboratory parameters. Response to treatment was observed in 19/37 (51%) patients, 16/24 (67%) in group T vs 3/13 (23%) in group NA ($p = 0.019$). Response was achieved in 15/24 (63%) patients with grade 1, 4/9 (44%) with grade 2, 0/4 with grade 3 ACLF ($p = 0.02$). Non responders had higher MELD-Na than responders (34 ± 5.2 vs 30 ± 5.4; $p = 0.03$). The type of vasoconstrictor [OR 5.88 (1.09–31.64); $p = 0.03$] was the only independent predictive factor of response to treatment. With respect to 28-day mortality, 18/19 (95%) responders to treatment were alive vs 7/18 (39%) of non-responders ($p < 0.01$). Leukocytes ($p = 0.01$), MELD-Na ($p < 0.01$) and ACLF grade 3 ($p < 0.01$) were also associated with 28-day mortality. Non response to treatment with vasoconstrictor and albumin was, together with MELD-Na [HR 1.17 (1.04–1.33; $p = 0.01$), the only independent predictive factor of 28-day mortality [HR 11.15 (1.35–92.12; $p = 0.025$)].
Conclusion: Terlipressin was far superior to noradrenaline in treating HRS-AKI in patients with ACLF and non response to treatment was the strongest independent predictor of 28-day mortality.

SAT138

Sarcopenia predicts mortality after transjugular intrahepatic portosystemic shunt creation in patients with refractory ascites

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Background and Aims: Loss of skeletal muscle mass is a common feature of patients with cirrhosis and predicts poor outcomes in candidates to liver transplantation. However, its association with mortality has not been fully studied in patients with cirrhosis and refractory ascites requiring transjugular intrahepatic portosystemic shunt (TIPS). Muscle area quantification at the level of third lumbar vertebra using abdominal computed tomography (CT) images is a novel technique for the evaluation of sarcopenia. Our study is aimed at evaluating whether CT-based assessment of skeletal muscle mass are associated with mortality after TIPS placement in contemporary patients with cirrhosis, severe portal hypertension and refractory ascites.
Method: We retrospectively reviewed the clinical information and pre-TIPS CT-images (within 3 months before TIPS creation) of all patients with cirrhosis and refractory ascites who underwent TIPS creation by using ePTFE covered stent at a single academic center in the period between January 2015 and November 2018. Evaluation of skeletal muscle mass was made by measuring the psoas muscle (PMA) and total abdominal muscles areas (TAMA), in a semi-automated way by using a specific software (Sliceomatic, Tomovision).
Results: 115 pts (78 male; 37 female, mean age 61 ± 9years) were included. Most frequent causes of cirrhosis were alcohol and non alcoholic steatohepatitis. Mean pre-TIPS MELD score was 12 ± 4 points. The average time between CT and TIPS creation was 56 days. Technical success of TIPS was 100%, and mean porto-caval gradient pre-TIPS and post-TIPS were 15.9 ± 4.4 mmHg and 6.5 ± 2.6 mmHg

Figure: (abstract: SAT138)

respectively. 16 patients died within 6 months of TIPS placement. Univariate analysis demonstrated that skeletal muscle mass (PMA and TAMA), as well as hemoglobin level, white blood cell count, serum albumin, serum bilirubin and MELD score pre-TIPS were strongly associated with 6-months mortality after TIPS. PMA had an area under the ROC curve of 0.702 for 6 months mortality and a PMA cutoff of 16 mm² (sarcopenia) was correlated with mortality. At multivariate Cox regression analysis sarcopenia, leucopenia, MELD score and PPG were independent predictors of post-TIPS 6-months mortality.

Conclusion: Sarcopenia, assessed on standard CT images of PMA, should be considered a risk factor for 6 months mortality in patients with cirrhosis who undergo TIPS placement for refractory ascites.

SAT139

Safety, tolerability, pharmacokinetics and pharmacodynamic activity of terlipressin delivered by continuous intravenous infusion in patients with cirrhosis and refractory ascites: a phase 2a open-label trial

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Background and Aims: Patients with cirrhosis and refractory ascites lack long-term pharmacological outpatient treatment options. The vasoconstrictor terlipressin, which is not yet available to US physicians, may reduce the accumulation of ascites but its approved uses, administered as bolus doses, are limited to the hospital setting and do not include the treatment of ascites. The pharmacokinetics of terlipressin administered as a continuous infusion is unknown and will be required to define the continuous infusion parameters.

Method: Six adult male patients with decompensated cirrhosis and ascites, requiring at least 3 large volume paracenteses (LVP) in the previous 60 days, and serum creatinine (SCr) <2.0 mg/dL were enrolled. Within 3 days after a LVP, patients started treatment with continuous infusion terlipressin administered via a PICC line by an ambulatory infusion pump with step-wise dose escalation (2 to 3 and then 4 mg/day over 5 days based on hemodynamic response and clinical safety). Following a 7 day in-house stay, patients continued treatment as outpatients with the highest tolerated dose of terlipressin for a total of 28 days. Serial plasma samples were collected through treatment and assayed for terlipressin and its more active metabolite, 8-lysine vasopressin, by LC-MS/MS.

Results: The mean **s**teady state plasma concentrations of terlipressin and 8-lysine vasopressin, 3.78 and 0.086 ng/mL, respectively, were lower than both peak and average plasma concentrations reported from previous studies following IV bolus administration. Consistent with low drug exposure, hemodynamic and cardiac tolerance was good during terlipressin infusion treatment and there were no adverse signs of tissue ischemia or clinically significant changes in daily ECGs. Three of the six patients completed 28-day infusion of terlipressin and three discontinued terlipressin infusion early for the following severe AEs: recurrence of Grade II hepatic encephalopathy, leak from a pre-existing umbilical hernia and progressive asymptomatic hyponatremia. Four of 6 patients experienced ≥50% increase in the interval between LVPs after the start of treatment with terlipressin, two of which experienced extended control of ascites beyond the 28 days of infusion for a total of 72 and 63 days, respectively. The volume of ascites removed by paracentesis in the 28 days prior to treatment versus the 28-day of the treatment period was reduced on average by 66%. Four patients experienced a rapid reduction in SCr levels during treatment.

Conclusion: The data supports the feasibility of long-term continuous IV infusion with terlipressin in the ambulatory setting given that it appears to be safe and well-tolerated at doses from 2 mg to 3 mg per day. Early pharmacodynamic and efficacy data are consistent with terlipressin infusion improving the underlying mechanisms resulting in ascites formation.

Child-Pugh score, median [range]	9 [7-11]
MELD-Na, median [range]	14 [9-22]
Age, years median [range]	61 [36-64]
LVP interval before treatment, days mean [range]	14 [6-21]
LVP interval during treatment, days mean [range]	34 [7–72]
Mean change in LVP interval	+ 134%
Total volume of ascites removed 28d before treatment, L mean [range]	26.25 [16.5–45]
Total volume of ascites removed during 28d treatment period, L mean [range]	12.1 [0–29]
Mean change in volume of ascites removed[a]	- 66%
Serum creatinine before treatment, mg/dL mean [range]	1.3 [0.9-2]
Serum creatinine during treatment[b], mg/dL mean [range]	0.9 [0.5-1.2]
Peak change in serum creatinine during treatment, mg/dL	- 0.36

a = during 28d treatment period vs. 28d before treatment, including baseline LVP ; b = D7 to D14

Figure: (abstract: SAT139)

SAT140

Salivary and stool microbiota differences are related to differences in 90-day hospitalizations in Mexican compared to American patients with cirrhosis

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Background and Aims: Stool and salivary microbiota are affected by diet, ethnicity and cirrhosis stage, which vary between countries and can affect 90-day hospitalization risk. Aim: Define effect of dietary and ethnic differences in salivary and stool microbiota across cohorts from USA and Mexico (MX).
Method: Age-matched controls and cirrhotic pts from US & Mexico underwent dietary recall, stool and salivary microbiota (16srRNA) analysis and were followed for 90 days for non-elective admissions. Comparisons between/within cohorts were performed. 90-day admissions predictors using microbiota, demographics, cirrhosis details/medications, and diet were performed separately for stool & salivary samples.
Results: 275 subjects (133 US & 143 MX) were enrolled from tertiary care centers in US & MX. Age, PPI use, MELD, ascites/HE were similar but there were fewer men in MX cohort.
Admissions: Higher in MX vs US (p = 0.03), most were liver-related (>70%) in both cohorts.
Diet: Lower protein and higher carbohydrate-rich diet in MX vs US. Similar vegetables, beef, rice but US subjects had higher coffee, tea, pork, milk, eggs, cheese and yogurt, with lower bread and fish in their diets compared to MX.
Microbiota: *Stool*: Significant differences with lower potentially beneficial taxa (Lachnospiraceae, Ruminococaeae) in MX with higher Prevotellaceae. *Saliva*: Prevotellaceae were higher in MX with lower Streptococcaceae & Lachnospiraceae. Porphyro/Veillo were similar between groups. *Diversity*: Stool and salivary diversity was lower in MX and reduced in both groups with advancing disease.
Regression: *Stool microbiota*: MELD (OR 1.2, p = 0.008) and Ascites (5.8, p = 0.01) were positively while vegetable intake (0.31, p = 0.03), and microbial families (Prevotellaceae 0.1, p = 0.008, Lachnospiraceae 0.1,p = 0.001, Veillonellaceae 0.1, p = 0.02, Ruminococcaceae 0.1, p = 0.05) were negatively linked with admissions. *Salivary microbiota*: MELD (OR 1.1, p = 0.04) and ascites(3.9, p = 0.06) were positively and Prevotellaceae (0.1, p = 0.01), Streptococcaceae (0.1, p = 0.002) and albumin (0.3, p = 0.02) were negatively linked with admissions.
Conclusion: Despite similar cirrhosis severity, Mexican cirrhotic patients had higher 90-day hospitalizations compared to Americans, which was related to significant differences in salivary and stool microbiota. Key microbial taxa such as Prevotellaceae and Lachnospiraceae were independently associated with this risk and could be modulated by dietary differences inherent between the cohorts.

SAT141

Validation of encephalapp stroop for minimal hepatic encephalopathy diagnosis in elderly patients with cirrhosis: a multi-center study

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Background and Aims: With the increasing age of patients with cirrhosis, current norms for minimal hepatic encephalopathy (MHE) testing, which usually are for younger patients, need to be recalibrated. **Aim**: Determine norms for EncephalApp Stroop & psychometric hepatic encephalopathy score (PHES) in elderly (>65 years) subjects with derivation & validation cohorts for MHE diagnosis.
Method: Subjects between 65 and 95 yrs were enrolled from 4 US centers. Healthy controls were those without chronic diseases. All pts

*p<0.05 US vs MX,†p<0.05 within USA ‡ p<0.05 within MX	USA (n=133)			Mexico (n=142)		
	Control(n=40)	Comp(n=50)	Decomp(n=43)	Control(n=41)	Comp(n=49)	Decomp(n=52)
Age	57.8±10.1	61.2±6.9	60.4±6.6	57.9±7.1	59.0±9.2	58.1±9.7
Male*	35%	80%	80%	30%	50%	50%
MELD score‡†	-	8.8±3.1	14.5±5.5	-	9.2±2.5	16.0±7.9
PPI use*†	20%	34%	47%	10%	20%	25%
Prior Ascites n(%) ‡†	-	-	29 (67%)	-	-	40 (76%)
Prior HE n(%) ††	-	-	35 (81%)	-	-	40 (76%)
Diet						
Yogurt*‡	23%	14%	16%	5%	4%	6%
Milk*‡	58%	50%	63%	31%	30%	17%
Chocolate*‡	28%	24%	36%	25%	8%	8%
Coffee*‡	58%	64%	67%	50%	38%	5%
Cheese*	68%	66%	67%	14%	18%	9%
Pork*‡	48%	82%	60%	64%	42%	24%
Fish*	58%	48%	42%	76%	52%	73%
Eggs*	55%	44%	50%	10%	26%	12%
Vegetables*††	92%	85%	79%	66%	48%	62%
Cereals	48%	34%	33%	59%	48%	66%
Breads*††	10%	6%	0%	57%	24%	36%
Hospitalizations over 90 days n(%)*††	-	5 (10%)	13 (28%)	-	1 (2%)	25 (48%)
Stool Microbiota(%relative abundance)						
Lachnospiraceae*††	20%	25%	14%	18%	15%	9%
Ruminococcaceae*††	12%	6%	4%	16%	12%	4%
Veillonellaceae*‡	0%	0%	1%	1%	1%	1%
Prevotellaceae*‡	0%	0%	0%	13%	27%	0%
Salivary Microbiota(%relative abundance)						
Lachnospiraceae*††	3%	3%	1%	1%	0%	0%
Streptococcaceae*	22%	27%	20%	20%	25%	19%
Veillonellaceae	7%	8%	7%	9%	9%	7%
Prevotellaceae*††	14%	20%	14%	28%	25%	18%
Porphyromonadaceae	1%	0%	0%	2%	0%	0%
Stool Shannon diversity*	1.7±0.4	1.6±0.4	1.5±0.4	1.7±0.3	1.5±0.3	1.3±0.5
Salivary Shannon diversity*	2.3±0.3	2.1±0.3	1.8±0.5	1.9±0.2	1.9±0.2	1.8±0.4

Figure: (abstract: SAT140): Demographic, clinical, dietary and microbial differences between groups.

	Controls (*n* = 99)	Patients with cirrhosis	
		Derivation cohort (*n* = 96)	Validation cohort (*n* = 77)
Age (years)	74.14 ± 6.46	70.32 ± 4.31 *	69.49 ± 4.36 *
Male (%)	42%	58%*	72%*‡
Education (Median [IQR])	16.0 [14.0, 18.0]	14.0 [12.0, 16.0] *	14.0 [10.0, 21.0] *
MELD score	–	10.8 ± 4.7	10.0 ± 4.0
Etiology (HCV/Alc/ NASH/other)	–	18/15/44/19	18/21/28/10
PHES components			
Digit symbol (low=poor)	56.56 ± 18.06	47.33 ± 15.74 *	43.51 ± 13.17 †
Number connection A (high=poor)	41.96 ± 31.47	47.94 ± 27.46 *	53.79 ± 27.35 †
Number connection B (high=poor)	103.94 ± 73.18	124.75 ± 85.89 *	130.36 ± 70.84 †
Serial dotting (high=poor)	59.56 ± 23.92	90.65 ± 45.02 *	80.11 ± 36.53 †
Line tracing (high=poor)	146.57 ± 48.20	138.90 ± 37.53 *	138.75 ± 40.63 †
EncephalApp Stroop			
Off+OnTime (high=poor)	193.27 ± 68.43	218.50 ± 78.66 *	215.19 ± 80.08 †
Mean (SD) unless otherwise mentioned, *p<0.05 controls vs derivation †p<0.05 controls vs validation, ‡p<0.05 derivation vs validation			

Figure: (abstract: SAT141)

had stable compensated disease. All subjects had MMSE>25 & could consent. Cirrhotic pts were enrolled in 2 cohorts; derivation: Enrolled between Mar'17–Sep'18 & validation: Oct'18–Oct'19. All subjects underwent PHES (5 tests, lower score = poor) &Stroop (OffTime +OnTime, higher time = poor). PHES/Stroop scores were compared between controls & derivation cohort pts and adjusted for on age, gender and education differences based on the controls enrolled. Cut-offs generated were used to diagnose MHE. Agreement between PHES & Stroop was studied & logistic regression was performed to assess the predictive power of Stroop on MHE on PHES (MHE-PHES). Regression equations from derivation were used for MHE diagnosis on the validation cohort.

Results: 99 controls (30 VCU 21 VA 25 Mayo 23 AR) and 96 pts (33 VCU 28 VA 10 Mayo 25 AR) were in the derivation cohort & 77 in the validation cohort (30 VCU 22 VA 20 Mayo 5 AR) (Table). Controls were younger, more educated & less likely to be men than both cirrhosis groups. Therefore, PHES & Stroop values were adjusted for age, gender & education. Apart from more men in validation, remaining demographics were similar to derivation cohort.

Cognitive performance on PHES and Stroop was worse in both cirrhosis groups compared to the controls. Validation & derivation cohorts had similar cognitive results.

MHE due to PHES & Stroop using adjusted cut-offs: For PHES, 6% of derivation cohort & 8% of the validation cohort had MHE. For Stroop, 53% of derivation & 49% of validation cohort had MHE.

Stroop vs PHES: If we considered PHES as gold standard, Stroop sensitivity in derivation cohort was 1.00, CI (0.93,1.00) with specificity 0.50, CI (0.92,1.00) while for the validation cohort sensitivity was 1.00, CI (0.61–1.00) & specificity 0.55, CI (0.43,0.66).

Logistic regression model predicting MHE-PHES by Stroop, the AUC for derivation cohort was 0.97, CI (0.89–0.99) with that of the validation cohort being 0.94, CI (0.86, 0.98).

Conclusion: Using derivation and validation cohorts of elderly cirrhotic patients in a multi-center study, age, education, and gender adjusted methods resulted in detection of MHE by Stroop in almost half the tested patients while MHE-PHES was significantly lower in prevalence. Age-specific norms are needed for accurate MHE diagnosis in the increasingly elderly population with cirrhosis.

SAT142

Lactulose withdrawal can potentiate breakthrough overt hepatic encephalopathy in patients controlled with rifaximin plus lactulose therapy: a post hoc analysis of a randomized controlled trial

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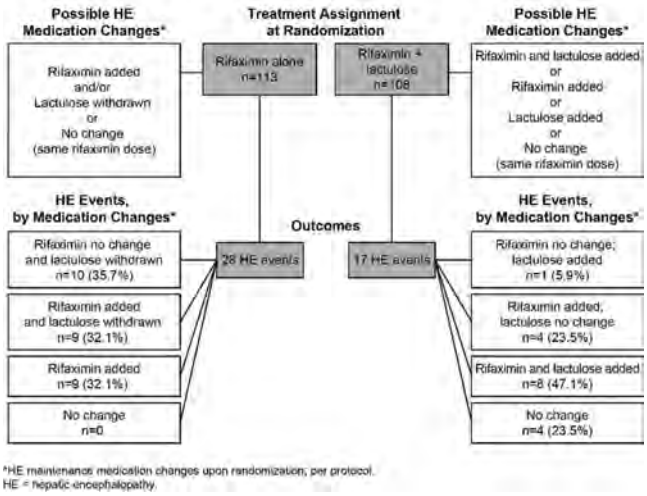
Background and Aims: Hepatic encephalopathy (HE) is a recurrent complication of cirrhosis. A post hoc analysis of a phase 4 trial of rifaximin alone vs rifaximin + lactulose explored the impact of HE medication changes necessitated by the trial on HE recurrence over 6 months (Clinicaltrials.gov identifier: NCT01842581).

Method: Eligibility criteria included adults with cirrhosis with a history of ≥1 overt HE episodes during the previous 6 months, currently in HE remission. HE maintenance medications were withdrawn from patients 1 day prior to random assignment to open-label rifaximin 550 mg twice daily (BID) or rifaximin 550 mg BID + lactulose (titrated to 2–3 soft stools/d) for 24 wks. The protocol-defined primary efficacy endpoint was time to first breakthrough HE episode. HE events were captured up to time of last patient contact. HE recurrences were analyzed post hoc based on HE medication withdrawal at randomization.

Results: 113 patients were in the rifaximin alone group, and 108 were in the rifaximin + lactulose group (Figure). At randomization, a greater percentage of patients assigned to rifaximin + lactulose group had rifaximin and/or lactulose added; conversely, a greater percentage of patients assigned to rifaximin alone group had lactulose withdrawn. In rifaximin alone group, 76 (67.3%) patients had lactulose withdrawn vs 0 in rifaximin + lactulose group. Rifaximin was added at randomization for 73 (64.6%) patients in rifaximin alone group and 81 (75.0%) patients in rifaximin + lactulose group; 39 (36.1%) patients in rifaximin + lactulose group had lactulose added. Breakthrough HE events in rifaximin alone group occurred most frequently in those who had lactulose withdrawn at randomization (19/28 [67.9%]), and the HE rate was higher than that observed for patients in rifaximin + lactulose group who continued lactulose (8/17 [47.1%]; Figure). None of the 9 patients in rifaximin alone group who were taking rifaximin prior to randomization (ie, no treatment change) had an HE event. Time to first HE breakthrough event data showed that rifaximin alone group had >2 times more HE events vs rifaximin + lactulose group (17 [15.0%] vs 7 [6.5%]) during the first 56 days postrandomization. In the rifaximin + lactulose group, the greatest percentage of patients with HE events were those with a history of HE who were not receiving lactulose or rifaximin HE prophylaxis at study entry; lactulose and rifaximin are recommended as prophylaxis for prevention of HE recurrence in AASLD/EASL practice guidelines.

Figure. HE Events Subgrouped by Medication Changes at Randomization*



*HE maintenance medication changes upon randomization, per protocol.
HE = hepatic encephalopathy.

Conclusion: Lactulose and rifaximin may play a synergistic role in prevention of HE recurrence. Withdrawal of lactulose at randomization, in conflict with guideline recommendations, was associated with a higher risk of HE recurrence in patients tolerating combination therapy in this study and may have affected study outcomes in rifaximin alone group.

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SAT143

Microbiome metabolic therapies reduce microbiota-associated ammonia in ex vivo fecal samples from healthy subjects and patients with minimal hepatic encephalopathy and demonstrate improved tolerability over lactulose in a clinical study

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Background and Aims: Microbiome Metabolic Therapies (MMT™) are novel synthetic glycans that have the potential to reverse dysbiosis associated with hepatic encephalopathy (HE) and reduce the gut contribution to blood ammonia levels, leading to improved clinical outcomes. We sought to identify an MMT that would reduce net ammonia and compared its tolerability to lactulose in Healthy Subjects (HS).
Method: Fecal samples from a HS were used to evaluate >200 MMTs in high-throughput *ex vivo* screens to assess their impact on bacteria-associated ammonia after 45 hrs of anaerobic growth. Further testing was done with fecal samples from a set of 28 HS and 25 pts with mHE (confirmed using either the Psychometric Hepatic Encephalopathy Score or Encephalapp Stroop in pts not on lactulose or rifaximin) incubated with MMTs selected from earlier testing.
We also conducted a clinical trial in HS comparing MMTs (MMT1, MMT2) titrated up to 90 g to lactulose (up to 40 ml tid) for short-term (~21 days) administration.
Results: MMTs were shown to lower both ammonia production and MDR pathogens in *ex vivo* screens. Subsequent testing of one of these MMTs showed significantly greater decreases in net ammonia than lactulose in samples from HS as well as those from patients with mHE (HS; 55% vs 41% reduction compared to control, $p < 0.001$; mHE: 37% vs 25% reduction $p < 0.001$).
In the clinical safety and tolerability study, 36 HS (12/grp) were randomized. There were no serious adverse events (SAEs). Three of twelve subjects receiving lactulose had temporary interruption of treatment due to gastrointestinal (GI) intolerance vs none receiving MMTs. All (12/12) subjects receiving lactulose had AEs (all GI, including diarrhea, abdominal distension) vs 7/12 in each group receiving MMTs (mainly GI, including abnormal GI sounds, headache). Seven subjects in the lactulose group had de-escalation of dose during the study vs one subject in each of the MMT1 and MMT2 groups. Daily stool frequency increased more from lactulose administration (from 1.2 to 2.4 stools/day) than from MMT1 (from 1.0 to 1.3) or MMT2 (from 1.1 to 0.8).
Conclusion: MMTs reduced microbiota-associated ammonia more than lactulose in fecal samples from HS and patients with mHE in an *ex-vivo* study. In a clinical study, fewer AEs and de-escalations of dosing were seen with MMTs versus lactulose. These results are promising and support further development of MMTs in HE.

SAT144

KB174 reduces relative abundance of multidrug resistance (MDR) enterobacteriaceae in fecal samples from patients with cirrhosis in an ex vivo test system

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Background and Aims: Patients with cirrhosis are at risk of infections, bacterial overgrowth and hospitalizations, in part due to a higher carriage of MDR organisms. These infections, such as spontaneous bacterial peritonitis (SBP), are often caused by gut-colonizing pathobionts belonging to the family *Enterobacteriaceae* translocating to ascitic fluid. With increasingly indiscriminate antibiotic use, the burden of infection from MDR organisms is mounting, resulting in a growing need for non-antibiotic strategies. Microbiome Metabolic Therapies (MMT™) are novel synthetic glycans that modulate the metabolic output of the gut through selectively enhancing growth of certain commensals. MMTs may reverse dysbiosis and could potentially be used for reduction of pathobionts that drive complications of infection in cirrhosis.
Method: Fecal samples from a healthy subject were incubated anaerobically for 45 hours with >200 MMTs in high-throughput ex vivo screens to assess their impact on bacteria-associated ammonia and the relative abundance of MDR pathogens. These pathogens were spiked in and included two carbapenem-resistant *Enterobacteriaceae* (CRE) strains of *E. coli* (CDC AR Bank #0001) and *K. pneumoniae* (CDC AR Bank #0003), and a vancomycin-resistant *Enterococci* (VRE) strain, *E. faecium* (ATCC 700221). Several MMTs demonstrated significant reductions in relative abundance of these pathogens. One MMT, KB174, was further tested for reduction of CRE *E. coli* which was spiked into fecal samples from 25 patients with cirrhosis who were not on lactulose or rifaximin and 19 healthy controls.
Results: KB174 was identified as a leading MMT that lowered both ammonia and MDR pathogens in *ex vivo* screens. Despite significant differences in community composition between healthy and cirrhotic fecal communities, incubation with KB174 led to significant decreases in the relative abundance of MDR *Enterobacteriaceae* (mean percent decrease, 43% ($p < 0.001$) and 50% ($p < 0.001$), respectively) compensated largely by significant increases of *Bacteroides* and *Parabacteroides* in both populations.
Conclusion: KB174 reduces the relative abundance of pathobionts in fecal samples from patients with cirrhosis. Based on these results, KB174 was investigated in a clinical study in cirrhotic patients (NCT03855956).

SAT145

Prevalence and clinical significance of portal vein thrombosis in cirrhotic patients with acute decompensation

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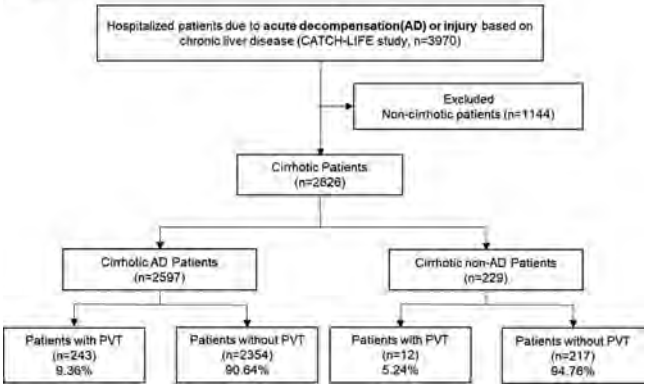
Background and Aims: Portal vein thrombosis (PVT) is a common and serious complication in cirrhotic patients. However, little is known about PVT in cirrhotic patients with acute decompensation (AD). We investigated the prevalence and clinical significance of PVT in nonmalignant cirrhotic patients with AD.

Method: Patients came from two prospective multicenter cohorts of patients with acute exacerbation of chronic liver disease, named CATCH-LIFE (NCT02457637 and NCT03641872), established by the Chinese Chronic Liver Failure Consortium from January 2015 to December 2016 and July 2018 to January 2019. The prevalence, clinical manifestations and risk factors of PVT in cirrhotic patients with AD were analyzed.

Results: The prevalence of PVT in cirrhotic patients with AD was 9.36%, significantly higher than those without AD (5.24%) ($p = 0.04$). Compared to cirrhotic AD patients without PVT, patients with PVT had a significantly higher incidence of variceal bleeding (47.33% vs 19.63%, $p < 0.001$) and a higher serum level of D-dimer ($p < 0.001$). Splenectomy, invasive procedures were independent risk factors for PVT in cirrhotic AD patients. The short- and long-term mortality rates of cirrhotic AD patients were significantly higher than those without AD ($p < 0.001$). But among cirrhotic AD patients, the short- and long-term mortality rates were similar between patients with PVT and without PVT.

Figure 1.



Conclusion: Cirrhotic patients with AD had a significant elevated prevalence of PVT. The occurrence of PVT promoted portal hypertension and variceal bleeding, thus would increase the risk for mortality as a result of the development of AD. It would be beneficial to improve portal hypertension through regular screening and preventing PVT in cirrhotic patients.

SAT146

Pre-emptive (early) transjugular intrahepatic porto-systemic shunt in the treatment of high-risk acute variceal bleeding. An individual patient data meta-analysis

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Background and Aims: Pre - emptive transjugular intrahepatic porto - systemic shunt (p - TIPS) within 72 h from acute variceal bleeding (AVB) reduced failure to control bleeding and rebleeding and showed better control of ascites without increasing hepatic encephalopathy in comparison to the use of endoscopic treatment plus drug therapy (E + P), in high-risk cirrhotic patients (defined as those with an HVPG ≥20 mmHg or with Child Pugh C less than 14 points (CP - C) or Child Pugh B with active bleeding during diagnostic endoscopy (CP - B + AB) despite vasoactive drug use). However, the survival benefit, although also consistently seen in CP - C patients, is less clear in CP - B + AB patients.
We aimed to investigate individual patient data from previous studies in order to re - evaluate the efficacy of p -TIPS versus standard - of - care, in terms of survival and post - treatment outcome in CP - C and CP - B + AB.
Method: The meta-analysis includes data from five previous studies: two randomized clinical trials and three observational studies. The analysis considers events that occurred in the first year after the index AVB, defined according to Baveno V Consensus. Adjusted models for risk evaluation were built using propensity score for baseline covariates. Multivariate Cox regression models were used to assess the predictive factors for survival.
Results: 1230 patients were included among whom 255 underwent p - TIPS and 975 E + P. Compared to E + P, p - TIPS reduced mortality in overall population (HR = 0.44; CI 95% [0.31–0.61], p < 0.000). This effect was powerfully demonstrated in CP-C patients (HR = 0.34; CI 95% [0.24–0.54], p < 0.000) and a strong trend was also observed in the overall CP - B + AB population (HR = 0.58; CI 95% [0.33–1.01], p = 0.056). In the CP - B + AB patients not receiving p - TIPS (n = 449), there was a significantly higher mortality in those patients with CP - B + AB >7 (n = 286) vs CP - B + AB = 7 (n = 163) (p < 0.000). In the subgroup of CP - B + AB >7 points, p - TIPS significantly improved survival (HR = 0.39; CI 95% [0.23–0.54], p < 0.000). p - TIPS also significantly decreased failure to control bleeding and rebleeding (HR = 0.34; CI 95% [0.25–0.45], p < 0.000) and "de novo" or worsening of previous ascites (HR = 0.23 CI 95% [0.18–0.41], p < 0.000). These effects were observed in both CP - C and in CP - B + AB patients. Compared with E + P, p - TIPS did not increase significantly the development of hepatic encephalopathy (HR = 1.15 CI 95% [0.89–1.50], p = 0.286). At multivariate analysis, adjusted by bilirubin, Child-Pugh class or MELD Score confirms that p - TIPS was an independent predictor of survival (p < 0.000).
Conclusion: In the setting of cirrhosis and AVB, in patients with CP - C < 14 points and in CP - B + AB >7 points, p - TIPS strongly improves survival and reduces rebleeding, failure to control bleeding and ascites without increasing the risk of hepatic encephalopathy and thus it represents the treatment of choice.

SAT147

Increased risk of perinatal complications in women with cirrhosis: a population-based matched cohort study

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Background and Aims: The number of reproductive-aged women with cirrhosis is rising. Details on perinatal complications related to cirrhosis are largely lacking. The aim of this study was to estimate the risk of obstetrical and neonatal complications in a contemporary cohort of women with cirrhosis compared to the general population.
Method: Retrospective population-based matched cohort study using routinely collected healthcare data in Ontario, Canada from 2000–2016. Pregnant women with cirrhosis who carried to at least 20 weeks gestation were identified using a validated cirrhosis case definition and routine mother-infant linkage. Women with cirrhosis were matched on age and socioeconomic status in a 1:5 ratio to pregnant women in the general population. Risk ratios between cirrhosis and perinatal complications were estimated using multivariate log-binomial regression adjusting for baseline diabetes, hypertension, obesity, dyslipidemia and co-morbidity with the Elixhauser Index.
Results: 2,098 pregnant women with cirrhosis were matched to 10,490 pregnant women in the general population; the median age was 31 years (IQR 27–34). Cirrhosis etiology was 70% NAFLD, 18% viral, 6% alcohol-related and 76 women (4%) had previous decompensation. Women with cirrhosis were more likely to have diabetes (11.6% vs. 8.2%, p < 0.001), hypertension (7.0% vs. 3.0%, p < 0.001), obesity (17.5% vs. 10.6% p < 0.001) and dyslipidemia (13.5% vs. 8.2%, p < 0.001) compared to those without cirrhosis. In adjusted models, cirrhosis was independently associated with large for gestational age infants, pre-term delivery, puerperal infections, and intrahepatic cholestasis of pregnancy (p < 0.05 for all, Table). Although the absolute difference in risk was low, compared to infants born to women without cirrhosis, infants born to women with cirrhosis were more likely to be stillborn (0.5% vs. 0.2%, p = 0.02) or die within 1 year of delivery (0.7% vs. 0.3%, p = .004).

Table: Risk of perinatal complications in pregnant women with cirrhosis compared to age and SES matched women without cirrhosis. Each outcome adjusted for baseline diabetes, hypertension, obesity, dyslipidemia and co-morbidity

Outcome	Risk Ratio	95% CI	P value
Large for gestational age (>90th percentile)	1.22	1.03–1.43	0.018
Pre-term delivery (<37 weeks gestation)	1.53	1.31–1.80	<0.001
Puerperal infections	1.38	1.08–1.76	0.010
Intrahepatic cholestasis of pregnancy	10.91	7.73–15.40	<0.001

SES: socioeconomic status.

Conclusion: Women with cirrhosis have higher risks perinatal complications compared to women in the general population even after adjusting for pre-existing co-morbid illness and metabolic risk

factors. These results support the involvement of multidisciplinary high-risk obstetric teams to manage pregnant women with cirrhosis and their infants post-partum.

SAT148

Does the wedge hepatic vein pressure estimates the portal pressure in patients with NASH cirrhosis?

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Background and Aims: The wedge hepatic vein pressure (WHVP) estimates the portal pressure (PP) in patients with cirrhosis. However, available evidence comes from studies performed in patients with hepatitis C virus (HCV) and alcohol-related cirrhosis. Therefore, it is unknown whether this correlation also exists in patients with cirrhosis due to non-alcoholic steatohepatitis (NASH-C). The aim of the study is to evaluate the correlation between PP and WHVP (PP-WHVP) in patients with NASH-C.

Method: Observational and retrospective study conducted in 3 European centers. We included patients with NASH-C treated with TIPS. Each patient was matched with two controls with HCV and alcohol-related cirrhosis (HCV/OH-C) who were treated with TIPS contemporaneously, adjusted for severity of liver disease. Patients with complete portal vein thrombosis or vein-to-vein communications that prevented a reliable measurement of WHVP were excluded. The PP–WHVP correlation was evaluated using the Spearman correlation (Rho) and the intraclass correlation coefficient (ICC). A PP–WHVP discrepancy ≥5 mmHg was considered significant. We compared between both groups the proportion of patients with significant PP–WHVP discrepancy and the proportion of patients in whom the hepatic venous pressure gradient (HVPG) failed to detect those with a portosystemic pressure gradient (PPG) ≥16 mmHg, a cutoff previously associated with high risk of death.

Results: So far, 93 patients have been included, 34 with NASH-C and 59 controls (34 OH, 25 HCV). The average age was 57 years and 75% were male. Reason for TIPS were variceal bleeding in 49% and refractory ascites in 43% of the cases. The PP–WHVP correlation was very good in the entire cohort (Rho: 0.818, CCI: 0.894), very poor in the NASH-C group (Rho: 0.617, CCI: 0.714) and excellent in the HCV/OH-C group (Rho: 0.906, CCI 0.957). The proportion of patients with significant PP–WHVP discrepancy was higher in the NASH-C group than in the HCV/OH-C group (15% vs. 3%, p: 0.095), being the PP underestimated by WHVP in the majority of the cases. The proportion of patients in whom HVPG failed to identify those with a PPG ≥16 mmHg was also higher in the group with NASH-C than in the group with HCV/OH-C (21% vs. 8%, p: 0.093).

Conclusion: In patients with NASH-C, the WHVP does not correlate with the PP as accurately as in other etiologies. The WHVP tends to underestimate the PP and may fail to truthfully assess prognosis in patients with NASH-C.

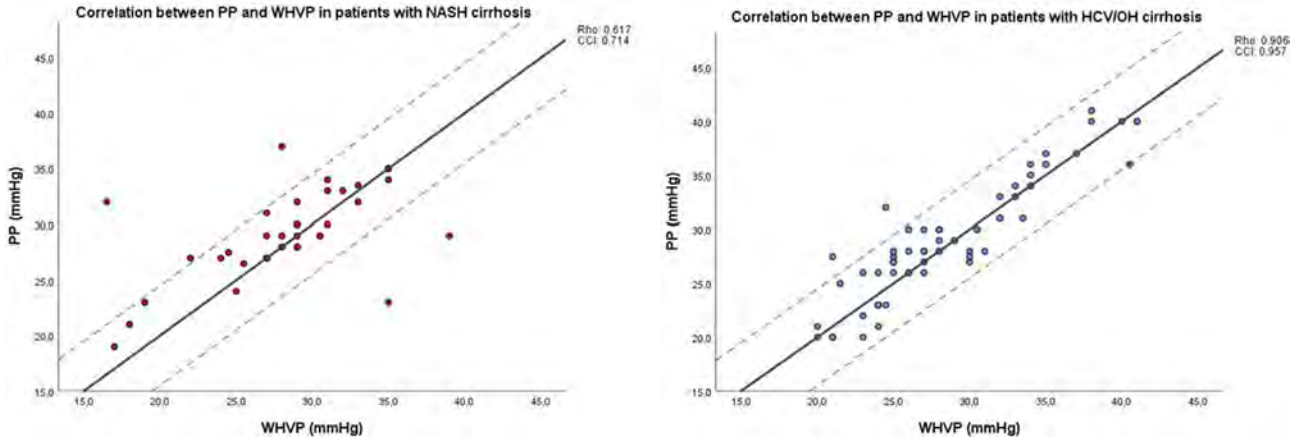

Figure: (abstract: SAT148)

SAT150

Prediction of variceal eradication in decompensated liver cirrhosis: a novel model

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Background and Aims: High risk esophagogastric varices (EGV) is common in decompensated liver cirrhosis and ties up with short-term variceal bleeding. Variceal eradication (VE) through endoscopic therapy has be recommended as the therapeutic goal of EGV treatment. However, factors associated with VE are not clear. In this study, we aimed to identify factors associated with VE as well as to develop a predictive model for better predication of VE.
Method: We carried out the case-control study based on an established prospective cohort conducted at The Third Affiliated Hospital of Sun Yat-sen University and patients with high-risk varices proved by endoscopy were screened. The primary endpoint was VE and patients achieved VE were classified as eradication group whereas patients transferred to other non-endoscopic therapies or did not achieve VE were classified as non-eradication group. Relevant medical and endoscopic data were collected. Comparisons between eradication and non-eradication group were performed by univariate and multivariate logistic regression to identify independent risk factors associated with failure in VE. Predictive model was developed and area under receiver operating characteristic (ROC) curve was calculated.
Results: A total of 468 patients were screened and 335 of them were included for the final analysis, with the mean age of 49 years. Two hundred and 89 cases (86.3%) successfully achieved VE through sequential endoscopic therapies combing band ligation, tissue glue injection and sclerotherapy, and median time to achieve VE was 5 months. In univariate analysis, non-eradication group had higher spleen size (cm) [P < 0.001], more ascites (P = 0.023), more portal vein thrombosis (PVT) (P = 0.020) and lower platelet count (P = 0.003). No statistical significant association was observed for liver function measured by Child-Pugh score or MELD score (P = 0.862 and 0.371, respectively), nor for the endoscopic findings including severity, extended length and red wale sign of EGV. In multivariate analysis, increased spleen size [hazard ratio (HR):1.20, P = 0.001] and PVT (HR:3.13, P = 0.016) were identified as the independent risk factors for the failure of VE, whereas ascites showed non-significant increased risk (HR:1.80, P = 0.081). A predictive model composed of the above three factors was established and the area under the ROC curve was 0.730 (95%CI: 0.653–0.807, P < 0.001).
Conclusion: Splenomegaly and PVT are highly associated with VE. Although the derived model will require external validation, it provides a useful new tool for clinicians to predict the probability of VE in cirrhotic patients and may help optimizing patient selection for endoscopic therapies.

SAT151

A comparison of non-invasive methods for the screening of gastroesophageal varices in patients with compensated cirrhosis

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Background and Aims: Baveno VI and American Association for the Study of Liver Diseases guidelines recommend that in compensated cirrhosis, screening for gastroesophageal varices (GOV) may be avoided in patients with a transient elastography (TE) score <20kPA and a platelet count (PLT) >150 × 10^9/L. Many centres however do not have access to TE. Recently, the RESIST-HCV criteria proposed that a serum albumin >3.6 g/dL and PLT >120 × 10^9/L predicted patients at low risk of varices needing treatment (VNT). We compared methods of non-invasive variceal screening to assess efficacy.
Method: Patients presenting to Monash Health (Victoria, Australia) for TE from 2011–2018 were prospectively recorded. Patients were included if they had compensated (Child-Pugh A) cirrhosis (TE >12 kPa). Exclusion criteria included: hepatocellular carcinoma, previous decompensation (GOV bleeding, ascites, hepatic encephalopathy), portal vein thrombosis or treatment with a non-selective beta-blocker. Patients were stratified according to Baveno VI, modified Baveno VI, expanded Baveno VI and RESIST-HCV criteria. Primary outcome was the absence of VNT defined as diameter >5 mm, grade ≥2 GOV, high-risk stigmata, or need for endoscopic treatment.
Results: 154 patients were included (41% Hepatitis C, 35% non-alcoholic fatty liver disease, 13% alcohol). The median age was 57 and median Child-Pugh score was 5. The median TE and PLT scores were 21 kPa and 160 × 10^9/L respectively. VNT were detected in 13 (8%)

Table 1: (abstract: SAT151) Performance of non-invasive screening methods

Criteria	Number in low-risk group	Number of VNT	Specificity	Sensitivity	Negative Predictive Value	P-value
Baveno VI **(TE <20 kPa, PLT >150)**	46 (30%)	1 (2.2%)	0.32	0.92	0.98	0.11
Modified Baveno VI **(TE<21 kPa, PLT >125)**	61 (40%)	1 (1.6%)	0.43	0.92	0.98	<0.05
Expanded Baveno VI **(TE<25 kPa, PLT >100)**	84 (55%)	1 (1.2%)	0.59	0.92	0.99	<0.001
RESIST-HCV **(Albumin >3.6, PLT >120)**	75 (49%)	3 (4%)	0.51	0.77	0.96	0.08

patients. The performance of non-invasive risk scores are detailed in Table 1.
Conclusion: Non-invasive methods can accurately risk stratify patients with compensated cirrhosis and 30%–55% patients may safely avoid screening endoscopy depending on the criteria utilised. Patients meeting the RESIST-HCV criteria have a <5% chance of having high-risk varices, comparable to the Baveno VI criteria. Thus, in facilities without access to TE, serum albumin and platelet count can accurately identify patients with a low-risk of varices who may safely avoid endoscopic screening.

SAT152

Pre-procedural blood product transfusion and bleeding predictors in patients with chronic liver disease undergoing elective invasive procedures at a tertiary liver unit

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Background and Aims: International guidelines recommend empirical blood product transfusions (BPT) prior to intervention in patients with chronic liver disease (CLD) based on standard coagulation tests. Our primary aim was to audit BPTs in patients with CLD undergoing invasive interventional procedures (IP). Our secondary aim was to identify factors that associate with bleeding complications.
Method: We undertook a retrospective audit of the electronic records of CLD patients who underwent any elective IPs between January and June 2019 at the Birmingham Liver Unit – a tertiary liver transplant unit in the UK. We evaluated BPTs against the international consensus guidelines available at the time (issued by the Society of Interventional Radiology and endorsed by the Cardiovascular and Interventional Radiological Society of Europe (SIR/CIRSE) in 2012), bleeding complications (BC), mortality and other complications.
Results: 154 procedures were performed [89 low- (LRP), 48 moderate- and 17 high-risk (HRP) by SIR/CIRSE stratification]. Demographics and aetiology were reflective of the chronic liver disease cohort in a developed country with: a mean age of 55, male predominance (70.1%) and dominated by alcohol related liver disease and non-alcoholic steatohepatitis (77.3%). 17/154 (11%) cases had abnormal clotting parameters that required correction; 7 (41.2%) (5 LRP) did not receive recommended correction. 2/137 (1.5%) patients with satisfactory parameters received unwarranted products. Overall non-adherence to SIR/CIRSE guidelines was 5.8%. 5 cases (2 LRP, 3 HRP) suffered a BC (3.2%). Neither platelets ($p = 0.346$), INR ($p = 0.287$) or adherence to guidelines ($p = 0.999$) correlated to bleeding on univariable regression ; however, bilirubin (OR 1.012, $p = 0.041$) and HRPs (OR 10.04, $p = 0.016$) did.
Conclusion: Current practice likely reflects growing acceptance of the inadequacy of standard clotting parameters to echo bleeding risk in CLD and mirrors subsequent SIR/CIRSE and AGA guidelines released in June and July 2019. Future use and study of other haemostasis measures (e.g. fibrinogen and thromboelastography) may advance clinical safety, reduce blood product use and provide cost savings.

SAT153

Urinary liver fatty-acid binding protein (UL-FABP) predicts acute-on-chronic liver failure (ACLF) and mortality in patients with decompensated cirrhosis

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Background and Aims: ACLF is characterized by acute decompensation of cirrhosis and organ failure(s) (OF). Considering its dismal prognosis, predicting the development of ACLF is essential. Currently there is no biomarker to predict the development of ACLF. L-FABP is a small protein that is highly expressed in the liver after tissue injury but is also expressed in other organs such as the kidney. We hypothesized that uL-FABP could be a biomarker to predict the development of ACLF in patients with decompensated cirrhosis. Our aim was to investigate the usefulness of uL-FABP as biomarker to predict ACLF and prognosis in patients with cirrhosis.
Method: Urinary L-FABP was measured at the time of admission in a prospective cohort of consecutive patients with cirrhosis admitted to hospital for complications of the disease. Clinical outcomes and survival were assessed over a 3-month period.
Results: A total of 305 patients were included (median MELDNa 21). 112 (37%) patients had ACLF at admission. uL-FABP was significantly higher in patients with ACLF compared to those without ACLF [median (IQR) 45 (18–89) vs 25 (14–60)μg/gr creat; $p = 0.005$]. Patients with liver, coagulation and circulatory failure showed significantly higher uL-FABP levels compared to those of patients without OF [liver: 80 (36–136) vs 25 (13–60), $p < 0.001$; coagulation: 65 (25–136) vs 28 (15–65), $p = 0.003$; circulatory: 81 (39–149) vs 25 (14–60); $p < 0.001$]. There were no significant differences in uL-FABP levels according to the presence or absence of respiratory, brain or renal failure. Nineteen (10%) out of the 194 patients without ACLF at admission developed it within 3 months. uL-FABP was independently associated with development of ACLF, together with MELDNa. The combination of uL-FABP and MELDNa were able to predict the development of ACLF with high accuracy (AUC 0.878). Interestingly, uL-FABP modulates the accuracy of MELDNa: patients with high uL-FABP had significantly higher probability of developing ACLF compared to those with low uL-FABP (40% if MELDNa ≥21 & uL-FABP>30 vs 10% if MELDNa ≥21 & uL-FABP<30; $p < 0.001$). Patients who died had significantly higher levels of uL-FABP compared to those who survived. In multivariate analysis, uL-FABP and MELDNa were independently associated with 3-month mortality.
Conclusion: Urinary L-FABP is a good biomarker to predict ACLF and mortality in hospitalized patients with cirrhosis. Our findings suggest that uL-FABP reflects liver and circulatory failure as main factors involved in ACLF development.

SAT154

Sarcopenia and liver cirrhosis: comparison of the European working group on sarcopenia criteria 2010 and 2019

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Background and Aims: Sarcopenia is prevalent in 30–70% of cirrhotic patients with a higher prevalence in men (61.6%) than in woman (36%). However, criteria for the diagnosis of sarcopenia are not universally accepted and several different definitions coexist. In 2010, The European Working Group on Sarcopenia in Older People (EWGSOP) provided consensus criteria for the diagnosis of sarcopenia using muscle mass, muscle strength and muscle performance as a practical clinical definition. In 2019, a revised definition was published based on the current evidence. It is yet unclear how these modified criteria influence the rate of diagnosis in high risk populations, such as liver cirrhosis.

Method: We therefore assessed if the new diagnostic criteria for sarcopenia impact on sarcopenia prevalence in liver cirrhosis. Within 2 years 114 cirrhotic patients were prospectively enrolled in the study. Sarcopenia was determined by muscle strength (handgrip strength), muscle mass (lumbal muscle index) and muscle performance (gait speed). We assessed the absence of sarcopenia (no sarcopenia group) or the presence of pre-sarcopenia or sarcopenia/severe sarcopenia using both 2010 and 2019 definitions.
Results: Based on the 2010 definition, 38/114 (33.3%) patients had no sarcopenia, 35/114 (30.7%) suffered from pre-sarcopenia and 41/114 (36%) from sarcopenia. With the 2019 definition, significantly more patients (91/114, 79.8%) were diagnosed as non-sarcopenic, whereas only 4/114 (3.5%) were diagnosed as pre-sarcopenia and 19/114 (16.7%) as sarcopenic ($p < 0.0001$). Indeed, when applying the 2010 definition, significantly more men were diagnosed as pre-sarcopenic ($p = 0.006$). Using the 2019 definition, the rate of pre-sarcopenia was significantly lower (30.7% versus 3.5%) due to the different starting points (2010 muscle strength, 2019 muscle mass) and cut-off values (muscle strength). Differences between regarding prevalences of sarcopenia when using the different diagnostic definition are summarized in a Sankey diagram also visualizing and quantifying the flow between groups (Figure 1).

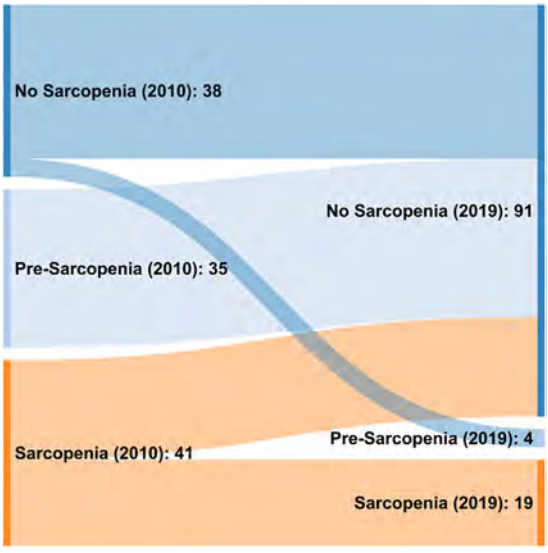

Figure: Sankey diagram to visualize and quantify the changes in sarcopenia diagnosis using the EWGSOP 2010 and 2019 criteria.

Conclusion: The change in diagnostic criteria for sarcopenia drastically influences the rate of pre-sarcopenia diagnosed cirrhotics. To evaluate, which diagnostic criteria should be chosen to diagnose sarcopenia in liver cirrhosis patients, prospective studies are needed.

SAT155

Validation of diagnostic usefulness of the spot urine Na/K ratio for replacement of 24-hour urine NA excretion in cirrhotic patients with ascites

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Background and Aims: The low salt diet is important for controlling ascites in patients with cirrhosis. 24-hour urine Na excretion test is standard method to determine the low-salt diet compliance. Measuring 24-hour urine Na excretion is a cumbersome method, so it is known that spot urine Na/K ratio can be measured instead. However, it is not fully validated that the spot urine Na/K ratio can replace 24-hour urine Na excretion. The purpose of this study was to validate whether the spot urine Na/K ratio could replace 24-hour urine Na excretion.
Method: A total 192 patients with liver cirrhosis and ascites were screened from multi-center. 175 patients were enrolled according to the inclusion criteria and prospectively studied. 24-hour urine collection was done and 5 mL of random urine was collected in the morning. 24-hour urine Na, creatinine, spot urine Na and K were checked. We confirmed the completeness of urine collection on the basis of 24-hour creatinine excretion over 15 mg/kg/day for men and 10 mg/kg/day for women. ROC curve analysis was performed to evaluate the feasibility of urine Na/K ratio for differentiating 24-hour urine sodium greater than 78 mmol/day.
Results: Only 57 patients were valid for urine creatinine excretion. Urine collections of 118 patients were invalid. There was no significant difference of age, sex, etiology of liver cirrhosis, Child-Pugh class, MELD score and psoas muscle thickness in two groups. In valid group, the area under ROC curve (AUROC) for random urine Na/K ratio in the prediction of 24 hr urine Na>78 mmol/day was 0.874 ± 0.051 ($P < 0.001$). In the invalid group AUROC was 0.832 ± 0.039 ($P < 0.001$). Both groups showed similar AUROC value. In valid group, the classical cut-off value over 1.0 of urine Na/K ratio showed 90.9% sensitivity, 56.0% specificity, 73.2% positive predictive value (PPV) and

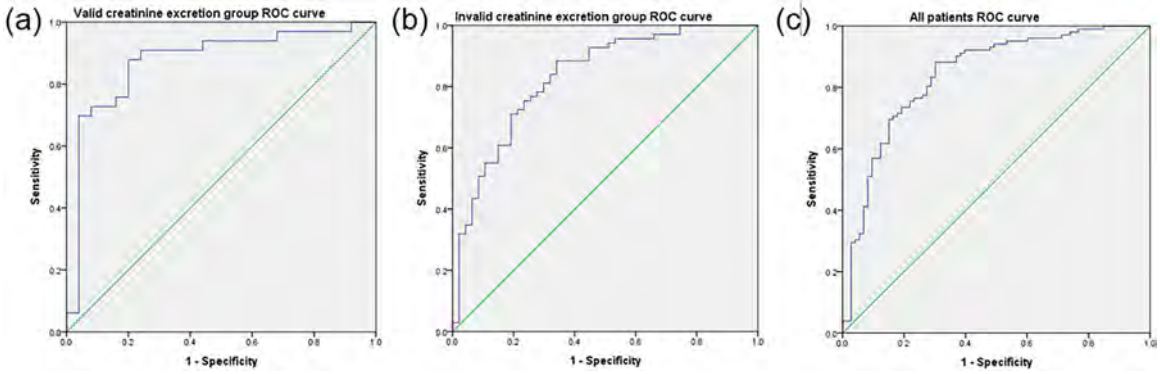

Figure: (abstract: SAT155): ROC curve of Na/K ratio in predicting 24 hour urine sodium excretion greater than 78mmol/day. (a) Valid group, (b) Invalid group, (c) All patients.

82.4% negative predictive value (NPV). The best cut-off point for Na/K ratio was 1.5, with 87.9% sensitivity and 80.0% specificity. In all patients, AUROC was 0.841 ± 0.031 (P < 0.001) and 94.1% sensitivity, 47.9% specificity, 71.6% PPV and 85.4% NPV on Na/K ratio 1.0 cut-off point. 131 patients collected urine during hospitalization. Valid urine collection did not differ between 34.4% in inpatients, and 29.5% in outpatients (p = 0.348).
Conclusion: The spot urine Na/K ratio reflects 24-hour urine Na, but ROC value in this study is lower than previous study. It is difficult to draw conclusions because the large number of incomplete urine collection. Even in hospitalized patients, there are many invalid collections, making it difficult to accurately check urine Na for 24 hours. Therefore, there is a need for a method to more easily identify low salt diet compliance in cirrhosis patients with ascites in the future.

SAT156
Proton pump inhibitor use is associated with an increased risk of hepatic encephalopathy in a large cohort of patients with cirrhosis
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Background and Aims: The incidence, etiology, clinical characteristics and survival of patients with liver cirrhosis in The Netherlands are yet poorly studied. Recent data suggested that use of proton pump inhibitors (PPIs) was associated with increased risk of hepatic encephalopathy (HE), whereas use of lipophilic statins could be associated with a decreased risk and better transplant-free survival (TFS). This study was performed to get insight in the incidence, etiology and course of the disease of patients with liver cirrhosis in The Netherlands and to detect factors, which could predict TFS and decompensation.
Method: Data of patients with liver cirrhosis from two large hospitals in Amsterdam were collected and analyzed for this study. Patients with confirmed cirrhosis, a follow-up time of >1 year and at least 2 visits at the outpatient clinic were included. Clinical parameters, use of medication, episodes of decompensation and other complications were extracted from the medical records.
Results: A total of 347 patients were included (67% males: median age 57 years (±12 years)) and median follow-up was 64 months (±60 months). Main etiology was alcohol use (29%) followed by chronic hepatitis C (18%). The median TFS was 159 months. At diagnosis, 31% of the patients had decompensated liver cirrhosis (Child-Pugh B 8 or more). Patients in the decompensated group were significantly older compared to patients in the compensated group (59 versus 56 years; p = 0.01). In 197 patients (57%) an episode of decompensation occurred during follow-up. Median TFS in the initially compensated group was 189 months compared to 99 months in the decompensated group (p = 0.01). Multivariate analysis showed that use of PPI was predictive for HE (HR 2.31 (1.23–4.34); p < 0.01). Statin use was not associated with decompensation or TFS. Sixty patients (17%) developed an hepatocellular carcinoma (HCC) during follow-up. These patients had a median survival of 25 months (±24 months) at time of HCC diagnosis. Patients with HCC screened adequately (52% of the patients) had a median TFS of 55 months compared to 24 months in the patients not screened adequately (p = 0.09).
Conclusion: Transplant-free survival of patients with decompensated and compensated cirrhosis was superior to that reported in the literature. Only half of the patients with HCC had participated in screening programs. PPI use was independently associated with development of HE.

SAT157
Quality improvement campaign led to higher surveillance rate for hepatocellular carcinoma in primary care clinic
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Background and Aims: The European Association for the Study of the Liver (EASL) recommends surveillance for HCC in cirrhotic patient by abdominal ultrasound every six months. However, various studies suggest that the surveillance rates in actual practice are quite low. The aim of this study was to evaluate the effectiveness of implementing quality improvement (QI) campaign in increasing the rate of HCC surveillance among patients with cirrhosis in primary care clinic.
Method: Patients with cirrhosis were prospectively enrolled into QI campaign. We engaged a network of clinic-based organizations and professionals in a 12-month campaign at primary care clinic to promote the adherence to EASL evidence-based practice guideline for cirrhosis, known to reduce the risk of cirrhotic complications. By using class room education program, social network communication and implemented standardized order sets for cirrhosis among providers at primary care clinic compare with control group at gastroenterology specialist clinic. Patients enrolled in this campaign between September 2018 and August 2019 were compared to cohort in February 2017 to January 2018. The primary endpoint was the receipt of at least one abdominal imaging study every 6 months, performed for the purposes of HCC surveillance during the study period.
Results: Of the 821 cirrhotic patients enrolled, 365 (44.4%) had imaging performed for HCC surveillance. In the campaign group, there was statistically significant increase in adherence to the HCC surveillance every 6 months (25.1% vs 41.2%, p <0.001). Compared to the non-campaign group, there was no significant increase in adherence to HCC surveillance every 6 months (45.4% vs 48.1%, p = 0.45). Direct health care costs were significantly increase in primary care clinic.
Conclusion: Implementation of QI campaign incorporating reminders of surveillance status for providers can significantly increase the rate of HCC surveillance among cirrhotic patients in primary care clinic.

SAT158
Calf circumference as an easy surrogate marker for the screening of Japanese patients with chronic liver disease
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Background and Aims: Chronic liver disease (CLD) is a typical disorder of secondary sarcopenia. Several sarcopenia guidelines recommend diagnostic imaging methods for assessing muscle volume. However, these are unsuitable for large-scale screening tests. Therefore, a simple screening method for sarcopenia is required. We analysed the usefulness of sarcopenia screening tests using calf and arm circumferences (CC and AC, respectively) in patients with CLD.
Method: This study was a single centre cross-sectional study. We analysed patients with CLD between April and October 2019. All patients underwent abdominal CT within 6 months. The skeletal muscle index (SMI) was calculated by dividing the cross-sectional area of the skeletal muscles (cm^2) at the third lumbar vertebra using

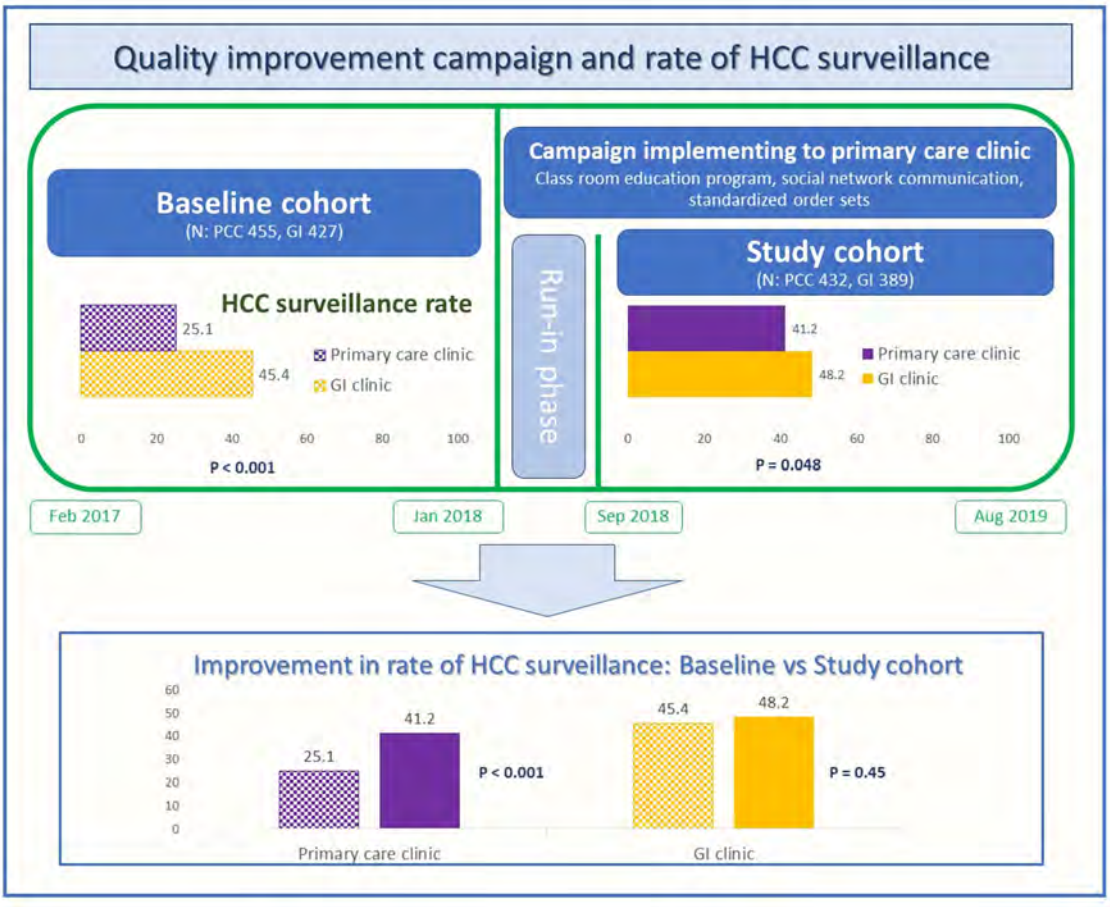
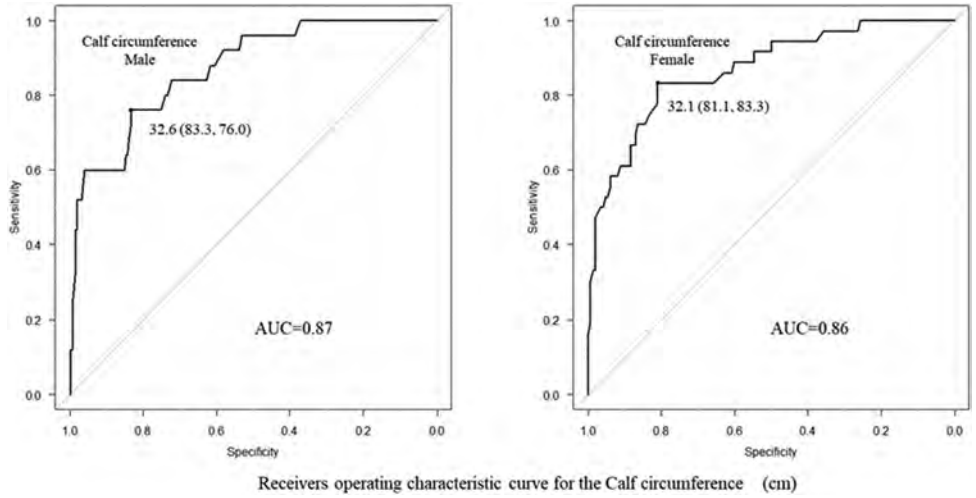


Figure: (abstract: SAT157)

CT by the square of the height (cm^2/m^2). Sarcopenia was defined according to the Japan Society of Hepatology (JSH) guidelines for sarcopenia using a liver disease algorithm, which includes both low muscle mass and strength. Low muscle mass was defined as an SMI <42 cm^2/m^2 and <38 cm^2/m^2 in men and women, respectively. Low muscle strength was defined as a grip strength <26 kg and <18 kg in men and women, respectively.

Results: Two hundred and thirteen patients were enrolled. The median age was 71 years, and 129 (60.5%) patients were male. In addition, 119 (55.9%) patients were diagnosed with liver cirrhosis. Low muscle mass and low muscle strength were found in 76 (35.7%) and 56 (26.3%) patients, respectively. Finally, 30 (14.1%) patients were diagnosed with sarcopenia. The sarcopenia group was significantly older (69 vs 77 years, P < 0.01) and had a higher cirrhosis ratio (80% vs



Receivers operating characteristic curve for the Calf circumference (cm)

Figure: (abstract: SAT158)

52%, P < 0.01) and lower serum albumin level (3.7 vs 4.1 mg/dL, P = 0.02) than the non-sarcopenia group. The sarcopenia group had significantly lower body mass index (21.3 vs 24.2 kg/m^2, P < 0.01), CC (29.5 vs 34.8 cm, P < 0.01), and AC (22.4 vs 26.3 cm, P < 0.01) than the non-sarcopenia group. SMI was positively correlated with AC (males, r = 0.68; females, r = 0.55) and CC (males, r = 0.68; females, r = 0.62). ROC analysis was performed to confirm the validity of AC and CC for sarcopenia, and the results identified areas under the curve of 0.87 and 0.86 for males and 0.87 and 0.80 for females, respectively. From ROC analysis, the optimal cut-off values of AC and CC were 24.4 cm and 32.6 cm for males (sensitivity, 84% and 76%; specificity, 78% and 83%) and 23.5 and 32.1 cm for females (sensitivity, 67% and 83%; specificity, 82% and 81%), respectively. In females, the CC was significantly more useful in distinguishing sarcopenia than the AC (P = 0.04). When the CC was 35.1 cm and 34.6 cm for men and women, respectively, the sensitivity and specificity were 96% and 53% and 94% and 50%, respectively.

Conclusion: CC was positively correlated with CT-measured SMI and could be used as an easy surrogate marker for the screening of sarcopenia in Japanese patients with CLD.

SAT159

A novel method: can stapedial acoustic reflex have a role in the diagnosis of minimally hepatic encephalopathy?

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Background and Aims: Stapedial acoustic reflex is an easily accessible and applicable test which is also valuable for the clinical conditions which affect the various locations of the central nervous system. Searching the diagnostic value of stapedial acoustic reflex at minimal hepatic encephalopathy is the aim of this research.

Method: Diagnosis of minimal hepatic encephalopathy was conducted by mini-mental state test and critical flickered frequency tests. Minimal hepatic encephalopathy diagnosed patients were established in the first group. Cirrhosis (without minimal hepatic encephalopathy or overt hepatic encephalopathy) diagnosed patients were created the control group. The stapedial acoustic reflex test was applied for minimal hepatic encephalopathy and the control group by audiologists in a soundproof room.

Results: In total 221 patients were screened and 97 patients meet the inclusion criterions. 52 patients out of 97 were the minimal hepatic encephalopathy patients and the remaining patients were created the control group. Acoustic reflex tests battery includes the evaluation of two pathways called ipsilateral and contralateral. Ipsilateral way test results were found positive in all minimal hepatic encephalopathy patients and 95% positive in the control group. Contralateral acoustic reflex test results were found 36% positive in minimal hepatic encephalopathy patients and 95% positive in the control group, respectively. Comparison of two group ipsilateral and contralateral acoustic reflex test results were displayed a statistical significance.

Conclusion: Stapedial acoustic reflex test results of cirrhosis patients may cover additional parameters for the diagnosis of minimal hepatic encephalopathy.

SAT160

Real-world treatment patterns and outcomes in hepatorenal syndrome: results from a retrospective chart review study in the United Kingdom

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Background and Aims: Hepatorenal syndrome (HRS) is a disease of impaired renal function in patients with advanced cirrhosis. The prognosis in patients with HRS is poor, with 50% patients surviving one month after diagnosis. European clinical practice guidelines recommend terlipressin in combination with albumin as the first-line

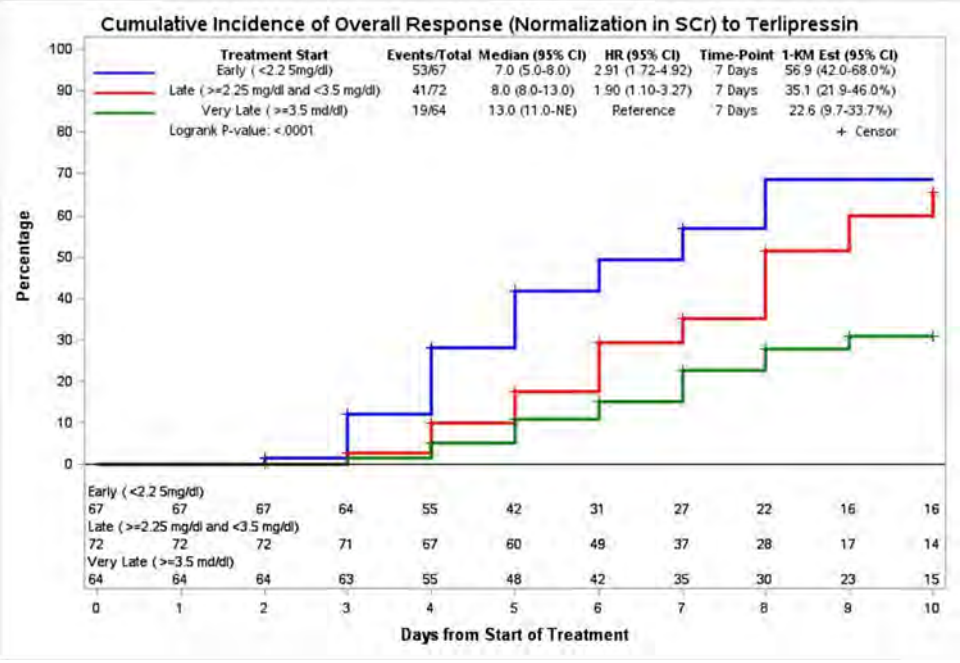

Figure: (abstract: SAT160)

treatment (tx) for HRS. However, quality real-world evidence on terlipressin use and its effectiveness are lacking. We conducted a retrospective, multi-centre medical chart study to assess tx and outcomes of terlipressin and other vasopressors (OVPs) for hospitalized HRS patients in the UK.

Method: Web-based case report forms were used to extract data of HRS patients treated with terlipressin or OVPs between Jan 1, 2013 and Dec 31, 2017. Collected data included patient characteristics, tx history, clinical outcomes and resource use. Changes in serum creatinine (SCr) from baseline post tx were used to assess clinical response (complete response [CR] if SCr ≤1.5 mg/dL; partial response [PR] if SCr reduction ≥20% but SCr >1.5 mg/dL). Descriptive analyses and Kaplan-Meier time-to-event analyses were conducted. Clinical response by tx initiation (SCr within 24 hours of admission, early SCr <2.25; late 2.25≤SCr<3.5; very late SCr ≥3.5) was also evaluated. The study complies with all EU data protection and privacy regulations.

Results: Data of 250 HRS patients was collected from 9 centres. 67% of patients were male and 72% were born before 1970. The majority of patients (80%) were treated with terlipressin monotherapy (72% in combination with albumin) on day 1 of admission with an average tx duration of 6 days. Overall response (CR and PR combined) was 73% for terlipressin monotherapy (n = 203) 59% for OVP monotherapy (n = 22), and 41% for vasopressor combinations (n = 25); CR rates were 50%, 23%, and 0%, respectively. Patients treated with terlipressin early had better cumulative overall response vs. late or very late (Figure 1). Patients with CR or PR were hospitalized for a shorter duration (median: 21.5 days) than patients with no response (median: 27.0 days). Terlipressin patients experienced the following precipitating events for HRS: diarrhoea (9%), gastrointestinal bleeding (28%), large-volume paracentesis (21%), spontaneous bacterial peritonitis (15%) and tx with diuretics (39%). Almost 79% of terlipressin patients had ascites. Common tx-attributable adverse events were fluid overload or pulmonary oedema (16% in TLP; 32% in OVPs) and multi-organ failure (9% in terlipressin; 9% in other OVPs).

Conclusion: This is the first real world study of patients with HRS in the UK. Terlipressin was the predominant tx for HRS in the UK. Clinical outcome results demonstrate that tx with terlipressin – especially early treatment – has a significant positive impact on patient outcome in the real world.

SAT161

Validation of HCC risk calculator in a UK centre and implications of thresholds for screening

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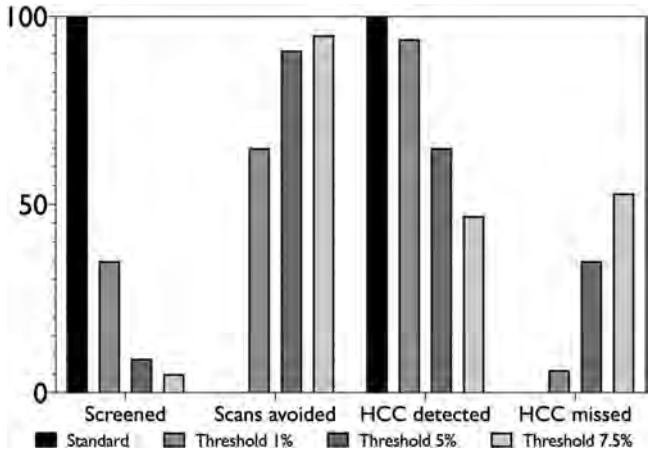
Background and Aims: hepatocellular carcinoma (HCC) is a complication of chronic liver disease. At present guidelines suggest that six monthly surveillance screening is offered to patients with cirrhosis to detect HCC although this is not based on trial evidence. A score to evaluate the risk of HCC was recently described in a US cohort (Ioannu et al J. Hep 2019 doi: doi.org/10.1016/j.jhep.2018.07.024.) We aimed to evaluate the accuracy of this score in our cohort of patients and to assess the implications of using thresholds or risk to guide surveillance.

Method: all patients in the stable cirrhosis clinic at Leeds Liver Unit with alcohol related liver disease (ArLD) or non-alcoholic fatty liver disease (NAFLD) had their HCC risk score calculated using the online calculator (hccrisk.com) at the time of the earliest available AST:ALT result. Patients were followed up with six monthly ultrasounds until the time of data collection or diagnosis of HCC. The proportion of patients who would have been screened at five-year risk thresholds of 7.5%, 5% and 1% were calculated along with the numbers of HCC that would have been detected or missed at each threshold. The accuracy of the HCC risk score was assessed by receiver-operator curve analysis.

Results: Two hundred and ninety two patients were scored: 105 had ArLD (36%) and 187 had NAFLD (64%). The average age was 63 years, 64% were male. The average 3-year risk was 1.25%, average 5-year risk was 2.12. Average follow-up was 3.12 years. In this time 17 patients developed HCC. The HCC risk score performed well with AUROC of 0.833 at three years and 0.844 at five years. In our cohort, using HCC risk thresholds of 1, 1.5, 5 or 7.5% would avoid 61, 34, 91 or 95% of scans respectively, at the cost of potentially missing 6, 6, 35 or 53% of cancers.



Conclusion: the HCC risk score performs well in our cohort. The risk of HCC in a dedicated compensated cirrhosis clinic is low in the majority of patients who fall below the conventional threshold for cost-effective surveillance (1.5%). Instituting this threshold would reduce the number of scans by 34% at the cost of 6% missed cancers.

SAT162

Liver stiffness by transient elastography to detect porto-sinusoidal vascular liver disease in patients with portal hypertension

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Background and Aims: Porto-sinusoidal vascular liver disease (PSVD) is a rare cause of intrahepatic portal hypertension. PSVD is still often misdiagnosed as cirrhosis, emphasizing the need to improve PSVD diagnosis strategies. The aims of this study were to evaluate the accuracy: (i) of liver stiffness measurement (LSM) using transient elastography (TE) to discriminate PVSD from cirrhosis in

patients with portal hypertension, and (ii) of Baveno VI criteria to rule-out varices needing treatment in patients with PVSD.
Method: We retrospectively included patients with PSVD, diagnosed according to the VALDIG criteria, from 2 University hospitals. We compared them with patients with histologically-proven compensated cirrhosis, related to alcohol or hepatitis C virus (HCV) infection, selected among the prospective French INCa CIRRAL and ANRS CirVir cohorts. All patients with PSVD and cirrhosis had clinical signs of portal hypertension and had reliable (according to EASL guidelines) LSM performed within a median (IQR) interval of 0 (0–3) months before or after diagnostic liver biopsy.
Results: Eighty-eight patients with PSVD (male gender 52%, median age 56 years, medium/large varices 37%, history of portal hypertensive bleeding 22%) were included. They were compared to 117 patients with alcohol-related cirrhosis (male gender 71%, median age 57 years, medium/large varices 13%) and to 110 patients with RNA positive HCV-related cirrhosis (male gender 61%, median age 53 years, medium/large varices 11%).
In patients with PSVD, LSM value [8.2 (6.2–12.7) kilopascals (kPa)] was significantly lower than in patients with alcohol-related cirrhosis [33.8 (21.3–62.7); $p < 0.001$], and than in patients with HCV-related cirrhosis [18.2 (13.9–26.7); $p < 0.001$]. LSM <10 kPa was able to diagnose PSVD when compared to alcohol-related cirrhosis or HCV-related cirrhosis with a specificity of 97% and 95%, respectively. LS>20 kPa was able to rule-out PSVD when compared to either alcohol-related cirrhosis or HCV-related cirrhosis with a specificity of 93% and 93%, respectively (Figure).

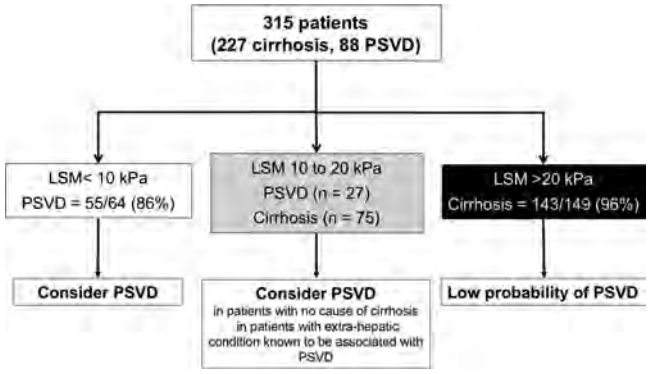

Figure: Probability of PSVD according to LSM values.

In patients with PSVD, Baveno VI criteria would potentially spare 36% endoscopies, but with an unacceptable risk of missing varices needing treatment of 29%.

Conclusion: In patients with signs of portal hypertension, LS <10 kPa strongly suggests PSVD as the cause of portal hypertension, particularly in the absence of cause for cirrhosis. Baveno VI criteria should not be applied to patients with PSVD.

SAT163
The utilisation of palliative care in patients with end-stage liver disease

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Background and Aims: End stage liver disease (ESLD) carries high morbidity and mortality. The only offer of cure is liver transplantation. The clinical trajectory of ESLD is often tumultuous with a high symptomatic burden that rivals advanced malignancy. Palliative care involvement in ESLD significantly improves subjective symptom scores and overall quality of life. Although the end of life care needs parallel those of acute renal failure and dementia, palliative care is largely underutilised in this population with referrals often occurring late and without documented goals of care. This study aims to identify the patterns of referral to palliative care for patients with ESLD in a tertiary hospital.
Method: Patients with ESLD who died from their disease and were referred to palliative care between 01/01/2018–31/12/2018, were identified retrospectively. Clinical information including cirrhosis aetiology, number of hospital admissions, decompensation events, MELD-Na and Child Pugh scores, symptom scores and timing of palliative care referral were obtained.
Results: 38 patients were included (81% male, 18.5% female). Alcohol was the most common cause of cirrhosis (31.6%) and 50% had hepatocellular carcinoma (HCC). At the time of referral to palliative care, 88.2% had performance scores translating to significant bed rest and care requirements. The predominant symptoms at referral were loss of appetite (52.9%), fatigue (50%) and pain (47.2%). 18% of patients were admitted to ICU in the same admission as the palliative care referral. There was no significant difference in the number of admissions pre-referral to palliative care between patients without or with HCC (3.5 vs 2.8, $p = 0.429$). Patients without HCC had significantly higher Child-Pugh (10.6 v 8.5, $p = 0.005$) and MELD-Na scores (23.1 v 18.5, $p = 0.049$) at the time of referral to palliative care. Patients without HCC had a significantly shorter survival following referral (17 days v 53 days, $p = 0.009$) and were predominantly referred for end of life care. The predominant trigger for palliative care referral in the HCC group was symptom control.
Conclusion: This study highlights that patients with ESLD are referred to palliative care at a lower level of baseline functioning and with high symptom burden. Referral patterns between HCC and non-HCC groups differed with non-HCC patients referred at a later stage and predominantly for end of life care, with shorter rates of survival. Palliative care is underutilised in patients with ESLD without a coexistent cancer diagnosis, leading to missed opportunities to improve symptom control and quality of life.

SAT164
Clinical features and outcomes of bacterascites in cirrhotic patients: A retrospective, multicenter study

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Background and Aims: Current guidelines on the management of bacterascites are limited because there are few studies on this topic. This multicentre, retrospective study investigated the clinical features and outcomes of cirrhosis patients with bacterascites.
Method: Two series of cirrhosis patients were evaluated. The first included 418 patients with ascites-positive cultures at 11 hospitals

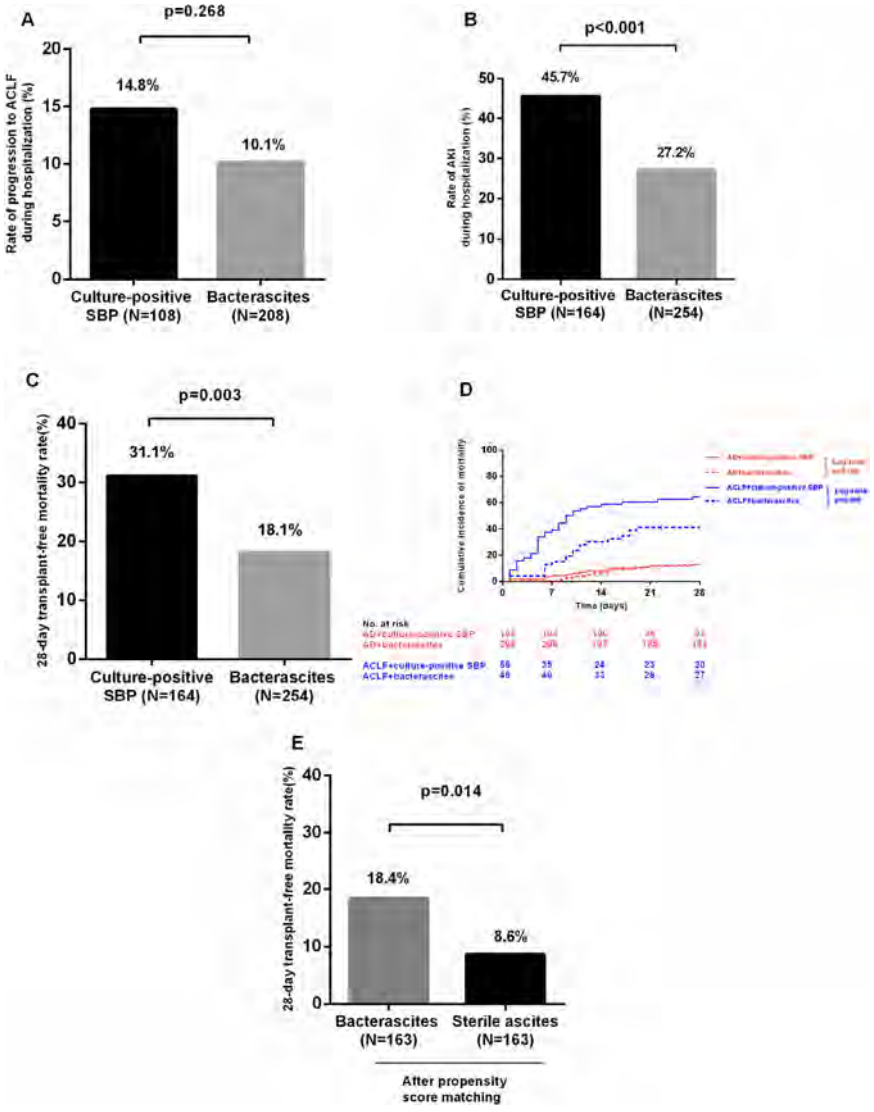

Figure: (abstract: SAT164)

during 2012–2018. Clinical characteristics and outcomes were recorded. The second series included 208 patients with sterile ascites from a prospective cohort (NCT02457637). Clinical features and outcomes of cirrhotic patients with or without bacterascites were investigated.

Results: In the first series, bacterascites was diagnosed in 254/418 (60.8%) patients, and culture-positive spontaneous bacterial peritonitis (SBP) was diagnosed in 164/418 (39.2%) patients. A total of 425 strains were isolated. Gram-positive bacteria were more prevalent in bacterascites patients than in culture-positive SBP patients (59.1% vs. 22.0%; $p < 0.001$). In this cohort, 33 patients had blood culture and the proportion of positive blood culture in bacterascites group was comparable with culture-positive SBP group (57.1% vs. 84.2%; $p = 0.084$). A higher prevalence of acute-on-chronic liver failure (ACLF) at the time of paracentesis was found in culture-positive SBP than in bacterascites patients (34.1% vs.18.1%; $p < 0.001$). For patients without ACLF, the probability of progression to ACLF within 28-day (10.1% vs 14.8%; $p = 0.268$) was comparable between bacterascites ($n = 208$) and culture-positive SBP patients ($n = 108$) (Figure A). The prevalence of in-hospital acute kidney injury (AKI) for bacterascites patients was 27.2%, which was lower than that of culture-positive SBP patients (45.7%; $p < 0.001$) (Figure B). The 28-day mortality rate was lower for bacterascites patients than for culture-positive SBP patients (18.1% vs 31.1%; $p = 0.003$) (Figure C and D), but it was much higher than that of patients with sterile ascites after propensity score matching (18.4% vs.8.6%; $p = 0.014$) (Figure E).

Conclusion: Bacterascites patients had non-negligible poor clinical outcomes, including in-hospital AKI, progression to ACLF, and 28-day mortality. Future studies are warranted to expedite the diagnosis of bacterascites and optimize antibiotic treatment.

SAT165

Continuous infusion of terlipressin for hepatorenal syndrome therapy: evaluation of efficacy and safety in real-life setting

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Background and Aims: Hepatorenal syndrome (HRS) is the most severe form of acute kidney injury (AKI) in patients with cirrhosis,

with high morbidity and mortality. Recent studies have shown that the terlipressin administration in continuous intravenous infusion appears to be as effective as its bolus use for HRS therapy, and with better tolerability. However, there is paucity of data with this strategy of administration for the treatment of patients with decompensated cirrhosis and HRS in real life setting.
Method: Prospective/retrospective cohort study in patients with decompensated cirrhosis non-electively admitted in two tertiary university hospitals from June 2018 to August 2019 who received continuous infusion of terlipressin in addition to albumin for the treatment of HRS. Clinical and laboratory characteristics of the patients, AKI stage, CHILD and MELD score, responses to treatment, adverse events, progression for liver transplantation and mortality were evaluated.
Results: A total of 25 HRS treatments in 18 patients were included in the study. Five patients (27.8%) had one or more recurrence of HRS after treatment withdrawal, in the same hospitalization on in subsequent ones, and all treatments were evaluated. Most patients were males (66.7%), with mean age of 57.5 ± 8.9 years. Alcohol (38.9%), followed by cryptogenic (22.2%), non-alcoholic steatohepatitis (16.7%) and chronic hepatitis C (16.7%) were the main etiologies of cirrhosis. Half of the patients had Child-Pugh score C, and MELD score ranged from 11 to 42. At HRS treatment initiation, ACLF grade was I in 83.4% of patients, and grade II in 11.1%, and AKI stage (S) was 1 in 44.4%, S2 in 27.8%, and S3 in 27.8%. Regarding all treatments, the mean terlipressin dose was 4.3 ± 2.5 mg, the treatment duration was 8.4 ± 4.7 days and the rate of complete response was 64%. Partial response was observed in 8% treatments, and no response in 28%. Of the latter, seven patients underwent renal replacement therapy. 38.9% of patients experienced adverse events while on therapy: 3 diarrhea, 1 abdominal pain, 2 bradycardia and 1 testicular ischemia (this one leading to treatment discontinuation). In-hospital mortality was 33.4%, and 5.5% were submitted to liver transplantation.
Conclusion: The administration of terlipressin in continuous infusion for HRS treatment seems to be a feasible and interesting option, with response to treatment and adverse events rates in line with previous reports in this scenario.

SAT166

Frailty assessed by the liver frailty index (LFI) predicts poor health-related quality of life (QOL) in patients hospitalised with liver cirrhosis

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Background and Aims: Cirrhosis has a detrimental effect on all domains of patient-reported outcomes (PROs) and QOL (Tapper 2018; Marchesini 2001). On the other hand, QOL is a good predictor of outcome and important target for intervention (Kanwal 2009; Tanikella 2010). Less is known about the determinants of QOL. Frailty is a global disorder impacting PROs beyond physical function (Lai 2014; Tapper 2019), is common in pts with cirrhosis, and is associated or correlates with poor QOL (Derck 2015; Carrey 2010). Association of the LFI (Lai 2017) – instrument from the newly recommended toolkit (Lai 2019) with QOL has not been studied yet. We aimed to determine the association of frailty with QOL and to identify predictors of poor QOL among pts admitted to hospital with liver cirrhosis.
Method: We prospectively enrolled hospitalized adults with cirrhosis from the HEGITO Registry. We recorded characteristics of pts demographics, liver disease etiology, complications, and disease stage; frailty and QOL were assessed at admission by LFI, and EQ-5D-5L™, respectively. Frailty was defined as LFI>4.5, QOL was expressed as a cumulative score of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with each assigned value from 1 (excellent) to 5 (poor). Poor QOL was defined as score worse (higher) than the 80th percentile.
Results: We enrolled 180 patients with all required parameters, with median age 57.7 years, 31.7% females, median MELD 17, and alcoholic etiology in 67.1%. Median LFI was 4.3 and 77 (42.8%) patients were designated as frail. Median QOL score was 8, QOL positively correlated with the LFI (r = 0.679, 95%CI 0.592–0.751, p < 0.001, Figure 1). Frail patients had a higher QOL score than non-frail patients (median 12 (25–75%, 11–14) vs. 5 (6–7). Patients with poor QOL had QOL score>14 and had significantly higher LFI, MELD, Child-Turcotte-Pugh score, C-reactive protein, lower mid-arm circumference, and were more likely to have refractory ascites and overt hepatic encephalopathy. In a multivariate logistic model, frailty (OR = 29.7, 95%CI 6.5–136.1) and refractory ascites (OR = 4.4, 1.64–12.0) were independent predictors of low QOL.

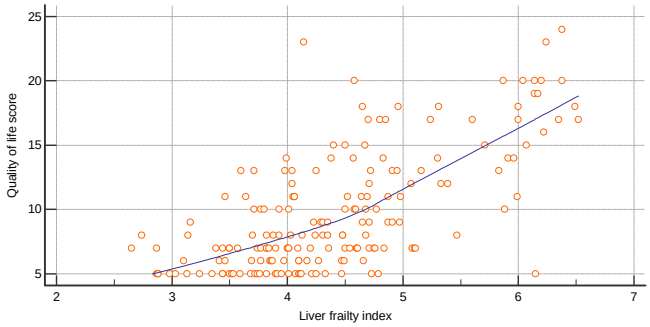

Figure 1. Correlation between liver frailty index and quality of life score (r = 0.679, 95%CI 0.592–0.751, p < 0.0001).

Conclusion: Low QOL among patients hospitalized for cirrhosis appears to be driven by frailty status and refractory ascites. Frailty is easily assessable by the LFI.

SAT167

A novel score to predict mortality after transjugular intrahepatic portosystemic shunt in patients with renal insufficiency

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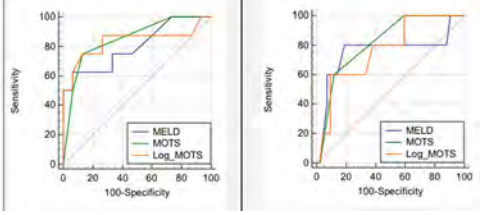
Background and Aims: The model for end-stage liver disease (MELD) is the best validated mortality predicting tool for patients undergoing transjugular intrahepatic portosystemic shunt (TIPS). However, with creatinine being one of three parameters, MELD may have limited validity in patients with renal insufficiency, inter alia, because renal function improves after TIPS. We aimed to develop a modified TIPS score (MOTS), based on MELD, but easier to calculate and of higher accuracy in patients with renal insufficiency.
Method: We retrospectively analyzed 113 cases of TIPS-placement at the University Hospital Graz. Creatinine was one of 11 parameters associated with 90-day mortality in univariate analysis. In multivariate analysis, only urea and INR were significant independent predictors. Thus, a score integrating urea, INR and bilirubin was developed. Cut-off-values were defined using Youden-Index of ROC coordinates. MOTS ranged from 0 to 3 points: INR >1.6, urea >70 mg/dl and bilirubin >2.2 mg/dl imply plus one point each. Additionally, inspired by the MELD score, a LogMOTS score was developed using continuous variables, to see whether it outlined the simple MOTS. Prognostic capability of the scoring models was assessed using Area Under Receiver Operating Characteristic (AUROC) statistics. The

scores were validated in an external cohort from the University Hospital Innsbruck (n = 188).
Results: In the total training cohort as well as the validation cohort, all three models significantly predicted 90-day mortality. AUROC values were MELD: 0.84 (95% CI:0.74–0.96), MOTS: 0.85 (0.74–0.96), LogMOTS: 0.79 (0.65–0.93) in the training cohort and MELD: 0.77 (0.62–0.93), MOTS: 0.80 (0.67–0.94), LogMOTS: 0.87 (0.79–0.96) in the validation cohort. 37 patients in our training cohort and 61 in the validation cohort had renal insufficiency defined as Estimated Glomerular Filtration Rate (eGFR) <60. In the training cohort, all three scores predicted 90-day mortality in patients with eGFR <60, whereas MOTS had the highest AUROC value. In the validation cohort, MOTS was the only model significantly predicting 90-day mortality in patients with eGFR <60 (Fig. 1).

Figure 1: 90-day mortality in TIPS patients with baseline GFR <60
statistical significance: [1]p= <0.05, [2]p= <0.01, [0] not significant

AUROC 90-day mortality	Training cohort (a)	Validation cohort (b)
MELD	0.77[1] (95%CI 0.57-0.97)	0.76[0] (95%CI 0.46-1.00)
MOTS	**0.85**[2] (95%CI 0.68-1.00)	**0.81**[1] (95%CI 0.64-0.98)
LogMOTS	0.83[2] (95%CI 0.62-1.00)	0.76[0] (95%CI 0.56-0.97)



Conclusion: With the simple MOTS, we developed a valuable tool to predict post-TIPS mortality, with higher accuracy than MELD in patients with eGFR <60. A continuous score with the same parameters had no beneficial prognostic value. To optimize future patient selection, prospective validation of MOTS is crucial.

SAT168

Differential activation of humoral compensatory mechanisms in distinct stages of portal hypertension

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Background and Aims: The arginine-vasopressin (AVP), brain-type natriuretic peptide (BNP), and renin/aldosterone systems represent critical regulators of hemodynamic homeostasis.
Method: We assessed plasma levels of copeptin (AVP biomarker), proBNP and renin/aldosterone in patients with advanced chronic liver disease (ACLD) stratified by portal hypertension (PH) severity, i. e. hepatic venous pressure gradient (HVPG) of 6–9 mmHg (n = 149, 19.1%), 10–15 mmHg (n = 211; 27.1%), and ≥16 mmHg (n = 419, 53.8%).

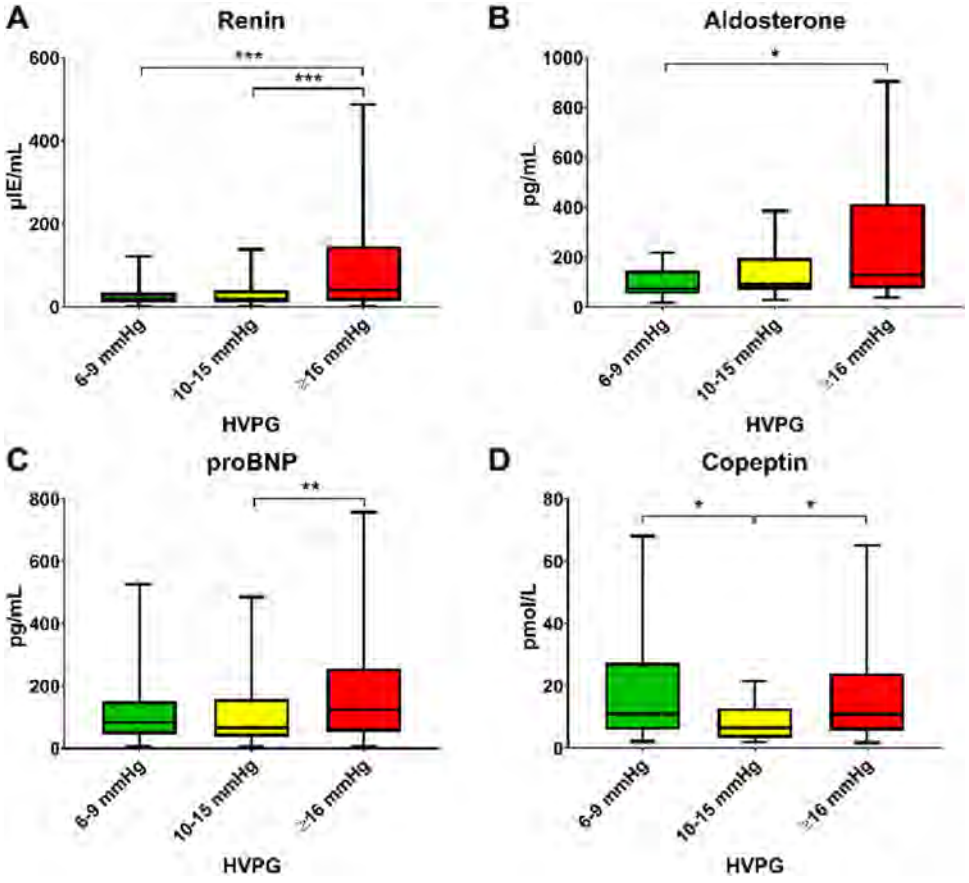

Figure: (abstract: SAT168)

Results: A total of 779 patients (age: median 56.9 years; Child-A: 58.3%, B: 29.7% and C: 12.0%) without intake of non-selective beta-blockers were included. With increasing severity of PH, higher heart rate ($p < 0.001$) as well as lower mean arterial pressure (MAP) ($p = 0.031$) and serum sodium ($p < 0.001$) indicated a hyperdynamic state. Hepatic dysfunction impacted on proBNP (Child-A: median 69.2 [IQR 88.3] vs. B: 149.7 [263.7] vs. C: 235.6 [424.0] pg/mL; $p < 0.001$), renin (Child-A: 15.6 [20.1] vs. B: 24.9 [173.2] vs. C: 136.5 [224.9] µIE/mL; $p < 0.001$) and aldosterone (A: 85.0 [84.0] vs. B: 167.0 [260.0] vs. C: 445.0 [867.7] pg/mL; $p = 0.004$).
When stratifying patients by HVPG (6–9, 10–15 and ≥16 mmHg), proBNP levels increased with PH severity (84.5 [106.6] vs. 65.9 [120.6] vs. 124.3 [203.5] pg/mL; $p = 0.004$). Moreover, both renin (18.0 [24.1] vs. 20.0 [30.4] vs. 39.9 [132] µIE/mL; $p < 0.001$) and aldosterone (74.0 [93.8] vs. 91.0 [126.0] vs. 127.5 [338.0] pg/mL; $p = 0.027$) gradually increased with HVPG.
AVP biomarker copeptin increased from Child-A: 7.2 [7.0], to B: 13.3 [21.1] and to C: 20.1 [44.3] pmol/L ($p < 0.001$), but showed no clear association with PH severity (HVPG 6–9: 11.0 [21.6] vs. HVPG 10–15: 6.5 [9.6] vs. HVPG ≥16 mmHg: 11.0 [18.4] pmol/L; $p = 0.012$).
Hyponatremia (<130 mmol/L) was associated with significantly increased levels of copeptin ($p < 0.001$), renin ($p < 0.001$) and aldosterone ($p = 0.003$), while proBNP ($p = 0.002$) and renin ($p < 0.001$) were significantly elevated in patients with severe hypotension (MAP <82 mmHg).
Conclusion: Severity of PH impacts on humoral compensatory pathways of systemic hemodynamic homeostasis as evident by proBNP secretion and renin/aldosterone activation, while the AVP axis is mainly influenced by hepatic dysfunction. In ACLD patients, arterial hypotension is linked to renin and proBNP release, whereas hyponatremia is linked to compensatory AVP and renin/aldosterone activation.

SAT169

Prospective study of magnetic resonance spectroscopy identifies specific metabolic changes in covert hepatic encephalopathy

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Background and Aims: Hepatic encephalopathy (HE) is a complex and significant neuropsychiatric complication of liver disease. An objective imaging technique would be valuable in the diagnosis, assessment and monitoring of HE. Recent meta-analysis data of Magnetic Resonance Spectroscopy (MRS) in HE suggests brain metabolite changes, particularly in the parietal region, could provide such a technique. This study aimed to prospectively describe the parietal MRS metabolite changes in cirrhotic patients with and without covert HE.
Method: This was a single-centre prospective cohort study initiated in 2018. Covert HE was defined using neuropsychological assessment: psychometric hepatic encephalopathy score (PHES) and continuous reaction time (CRT). The participants were stratified into three groups; cirrhosis with covert HE (CHE) (PHES<–4 +/– CRT-index<1.9); cirrhosis without HE (NHE) (PHES ≥-4 +/– CRT-index>1.9); and healthy controls (HC). Participants underwent: single voxel MRS was performed in the parietal region on Philip 3.0T MRI scanner and metabolite parameters were obtained using LC-model software (v5.3-1M); electroencephalography (EEG); assessment of liver function; serum ammonia, metabolomic and cytokine ananlysis; and chronic liver disease questionnaire (CLDQ). Statistical analysis was performed using IBM SPSS (v25).
Results: A total of 35 patients (mean age 62 years; male 71%) were recruited: CHE (n = 14); NHE (n = 12); and HC (n = 9). The parietal glutamine/creatine (Gln/Cr) ratio was significantly higher in both MHE 1.19 vs HC 0.28 ($p < 0.001$); and NHE 0.49 vs HC 0.28 ($p = 0.02$). PHES scores were found to be negatively correlated with glutamine/creatine (Gln/Cr) ($r = –0.6$, $p < 0.001$) (see Figure 1) and positively correlated with myoinositol/creatine (Ins/Cr) ($r = 0.6$, $p < 0.001$) and choline/creatine (Cho/Cr) ($r = 0.47$, $p = 0.004$). NHE was also associated with a similar attenuated pattern of metabolite change. This MRS metabolite pattern was associated with higher MELD scores, higher ammonia levels and lower CLDQ scores.

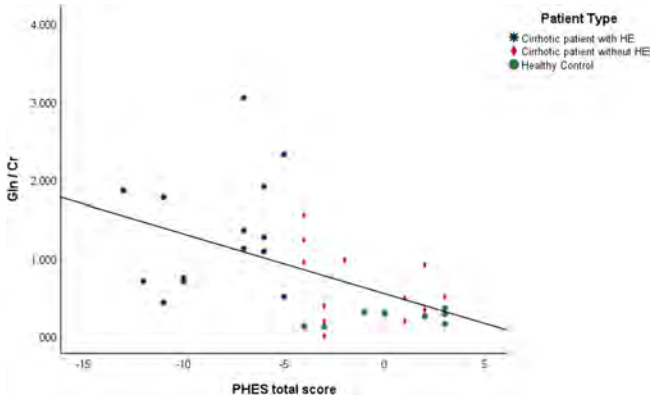

Figure: Correlation of PHES with glutamine/creatine (Gln/Cr).

Conclusion: MRS identified a specific parietal region metabolite signature with increased glutamine, reduced myo-inositol and choline, which correlated with the severity of HE. Significantly, NHE also had these identifiable changes. This MRS signature could provide an objective tool in the assessment and management of HE.

SAT170

Bacterial infections correlate with poor prognosis in cirrhosis independently from liver disease severity

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Background and Aims: Patients with cirrhosis are at increased risk of bacterial infections, which are among the most common reasons for decompensation, hospitalization and death. In recent years, evidence is growing on the dismal prognosis following an episode of infection in such patients. However, most of the studies have a retrospective design and include heterogeneous cohorts of patients. The aim of this study was to assess the prognostic significance of infections on long-term survival in a prospective cohort of patients with cirrhosis requiring hospitalization.
Method: We prospectively included consecutive cirrhotic patients admitted for at least 48 hours to a tertiary referral center over a 31 months period. Patients with hepatocellular carcinoma outside Milan criteria, extra-hepatic conditions with limited life expectancy, HIV infection, myeloproliferative diseases or previous organ transplantation were excluded. Infections were diagnosed on the base of positive cultures or strict clinical criteria. We used Cox-regression analysis for the identification of the most important predictors of long-term outcome.

Results: 254 patients (66% male, 56% alcoholic cirrhosis, mean Model for End-Stage Liver Disease (MELD) score = 15) underwent 392 admissions over the study period. Manifest hepatic decompensation (35.4%) (hepatic encephalopathy (12.4%), jaundice (5.8%) or ascites (17.2%)) and variceal bleeding (19%) were the main reasons for admission, followed by infections (18.5%). Considering the number of admissions, the prevalence of bacterial infections was 50.3% (52.3% community-acquired, 11.2% health-care associated, 36.5% nosocomial). Urinary tract infections were the most frequent infections (25.4%), followed by spontaneous bacterial peritonitis (22.3%), pneumonia (17.3%), sepsis (16.7%) and soft tissue and skin infections (7.6%). Overall, survival was independently associated with MELD score (hazard ratio (HR) 1.05; 95% confidence interval (CI) 1.02–1.08; p = 0.001) and bacterial infection (HR 1.63; 95%CI 1.02–2.59; p = 0.039). When excluding early deaths (30 days), patients with infections still showed a lower survival (p = 0.048) and a tendency to a higher mortality risk (HR 1.53; 95%CI 0.94–2.51, p = 0.086). MELD score remained significantly and independently associated with survival (HR 1.04; 95%CI 1.00–1.07, p = 0.02). Bacterial infection remained an independent predictor of poorer outcome across all stages of liver disease and mortality risk in patients with MELD score<15 and infection was comparable to that of patients with MELD score equal or higher than 15 who did not have infections.

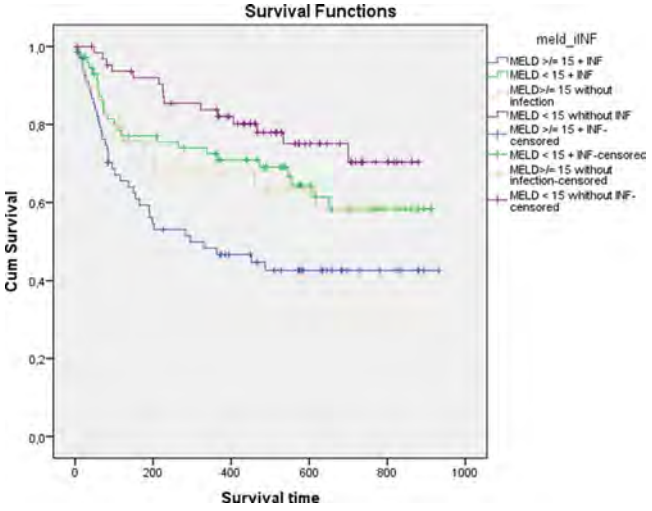

Figure: Kaplan Meier survival curves according to MELD score and the presence of infection (p = 0.001).

Conclusion: Bacterial infections represent a risk factor for increased long-term mortality in patients with cirrhosis independently from the stage of liver disease.

SAT171

Long-term albumin administration is not futile in patients with cirrhosis and uncomplicated ascites not normalizing serum albumin concentration with treatment

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Background and Aims: The benefits of long-term human albumin (HA) administration to patients with cirrhosis and ascites seen in the ANSWER trial[1] were associated to a significant increase of serum albumin concentration (SA). A subsequent post-hoc analysis[2] showed that survival probability increases in parallel with the on-treatment SA at month 1 and optimal results follow the attainment of normal SA.

This study aimed to determine whether patients randomized to the standard medical treatment plus HA arm (SMT + HA) in the ANSWER trial who failed to normalize on-treatment SA (≥3.5 g/dl) at month 1 have any advantage as compared to those receiving SMT alone.

Method: Patients not normalizing on-treatment SA at month 1 were matched with those enrolled in the SMT arm alive at 1 month by using a propensity score technique. The baseline variables independently associated to mortality according to a multivariable logistic regression (SA, MELD and Child-Pugh scores) were used to match the two groups. Survival analysis was performed with Kaplan-Meier method and Cox regression. The incidence rates of complications were computed by the exact method based on the Poisson distribution.

Results: In SMT+HA arm, 40 patients (21%) failed to reach the lower normal limit of SA at month 1, and were compared with 40 patients receiving SMT alone selected by the propensity score. Ten patients died in SMT+HA and 17 in the SMT arm, so that the 40 patients who received HA had a significantly higher 18-month overall survival (K-M estimates: 61.3% SMT + HA vs 36.7% SMT; p = 0.0315), corresponding to a 57% reduction in mortality HR (0.43 [95%CI 0.19–0.95], p = 0.036). These patients also showed a significant reduction in the incidence rate ratio of paracentesis (0.62 [95%CI 0.47–0.82], p < 0.001) and some complications of cirrhosis, namely spontaneous bacterial peritonitis (0.33 [95%CI 0.14–0.64], p < 0.001), hepatic encephalopathy grade III/IV (0.41 [95%CI 0.22–0.73], p = 0.001), and hyponatremia (0.43 [95%CI 0.25–0.72], p < 0.001).

Conclusion: Patients who failed to normalize SA during long-term HA administration had a clear benefit in terms of survival and occurrence of complications as compared to those only receiving SMT. Thus, HA treatment cannot be considered futile in this patient subset. Rather, this observation suggests that an increase in the HA dosage can be considered in order to reach on-treatment SA associated with better outcomes.

References

1. *The Lancet* 2018;391:2417–29.
2. *J Hepatol* 2019;70:e53.

SAT172

Subtle changes of serum creatinine and C-reactive protein during the index hospitalization predict early readmission in patients with decompensated cirrhosis

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Background and Aims: Patients with decompensated cirrhosis had a high risk of early re-hospitalization, thus carrying a heavy socio-economic burden. The present study aims at identifying new predictive factors and the prognostic impact of readmission within 30 days (early readmission) after discharge from an index hospitalization for acute decompensation (AD).
Method: Three hundred twenty-nine patients discharged after hospitalization due to AD were included in this prospective observational study. Laboratory and clinical data at admission, during hospital stay and at discharge of the index hospitalization were collected. Readmissions and its causes and mortality were recorded up to 1 year.
Results: Cumulative incidence of readmission was 18% at 30 days (early readmission), 39% at 90 days and 63% at 1 year. Early readmission was associated with a higher 1-year mortality (54% vs 33%, p = 0.001). The most frequent causes of early readmission were bacterial infection (21%), hepatic encephalopathy (19%) and ascites (19%). Data collected both at admission (Child-Pugh score, MELD-Na score, diabetes), during hospital stay (development of acute-on-chronic liver failure) and at discharge (MELD-Na score, platelet count, days spent in hospital) were significantly associated with early readmission.
We then investigated if subtle changes of routine laboratory parameters assessing liver and renal function and inflammatory response between admission and discharge were associated with early readmission. Multivariable competing risk regression analysis showed that increases as small as 0.2 mg/dl of serum creatinine and C-reactive protein (CRP) were associated with an increased hazard ratio (HR) of early readmission (serum creatinine: HR = 1.9 [95%CI 1.1–3.2], p = 0.034; CRP: HR = 1.8 [95%CI 1.1–3.2], p = 0.031). Such increase in serum creatinine was also associated with a higher 1-year probability of death (59% vs 31%, p < 0.001).
Conclusion: Almost one patient out of five is readmitted within 30 days after a hospitalization due to AD of cirrhosis. Besides already established parameters related to the severity of disease, even subtle increases in serum creatinine and CRP (0.2 mg/dl) between admission and discharge emerged as new risk factors for early readmission and worse prognosis, thus identifying patients who need for closer surveillance after discharge.

SAT173

Value of Hitachi shear wave elastography (SWE) for exclusion of esophageal varices in patients with compensated advanced liver disease

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Background and Aims: Liver stiffness (LS) assessed by Transient Elastography (TE) in combination with platelet count was introduced in the Baveno VI consensus in order to guide the need for gastroscopy for esophageal varices screening in patients with compensated advanced liver disease (cALD). According to the Baveno VI consensus, screening gastroscopy is not necessary if LS <20 kPa and platelet count is >150000 cell/mm^3. However, TE has a rate of failed measurements of approx. 10% and cut-off values obtained with M and XL probe vary substantially.
Method: Liver stiffness (LS) was measured with Hitachi SWE (Arietta V70) and Transient Elastography (TE) (FibroScan®, Echosens, France). According to Ferraoli et al (J Gastrointestin Liver Dis 2017; 2: 139–143) a SWE LS cut-off value >9.15 kPa rule-in the presence of liver cirrhosis, while a cut-off value <8.4 kPa rule-out the cirrhosis. Reliable LS measurements with both methods were defined as median value of ten valid measurements with an IQR/Med <30% and expressed in kilopascals (kPa). Recent gastroscopy (not older than six months) had been conducted in all patients. The performance of the Baveno VI criteria and the performance of LS, assessed by Hitachi SWE in combination with platelet count, for ruling out esophageal varices were analyzed.
Results: Our cohort included 91 patients with cALD with a mean age of 58.7 ± 12.5 year, 67% men. 54.9% had an alcoholic etiology. Esophageal varices were diagnosed in 46.1% of the patients. The rate of reliable measurements was 98.9% for Hitachi SWE and 93.4% for TE. None of the patients with esophageal varices had LS assessed by TE <20 kPa and platelet count >150000 count/mm^3, showing a very good performance of the Baveno VI criteria. LS assessed by Hitachi SWE was significantly higher in the cohort of cALD patients with esophageal varices as compared with those without varices: 14.1 ± 4.3 kPa vs. 11.3 ± 3.8 kPa, p = 0.001. A combination of LS as assessed by Hitachi SWE (values <10.6 kPa) and platelet count >150000/mm^3, could non-invasively successfully rule-out the presence of esophageal varices in 90/91 patients (98.9%).
Conclusion: LS assessed by Hitachi SWE in combination with platelet count seems to be a good method to rule-out the presence of the esophageal varices in patients with cALD.

SAT174

Factors associated with the presence of cirrhotic cardiomyopathy defined according to the new multidisciplinary diagnostic criteria

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Background and Aims: The prevalence and associated factors of cardiomyopathy in cirrhotics remain unknown. Recently published new criteria of cirrhotic cardiomyopathy from a multidisciplinary consortium (Izzy et al. Hepatology 2019 Nov 11. doi: 10.1002/hep.31034) define systolic dysfunction of the left ventricle as ejection fraction (EF) ≤50% and/or global longitudinal strain (GLS) <−18 or > −22%, while the diastolic dysfunction is diagnosed when three of the following conditions are present: average E/e' >14, peak tricuspid regurgitation velocity >2.8 m/s, septal e'<7 cm/s, left atrial volume index >34 ml/m^2.
Our aim was to assess the factors associated with the presence of cirrhotic cardiomyopathy defined according the new diagnostic criteria.
Method: Consecutive patients with liver cirrhosis without structural heart disease, HCC outside Milan criteria, presence of TIPS and with

optimal acoustic echocardiography window were included. Conventional and speckle-tracking echocardiography (Vendor GE, EchoPAC PC software) were performed by a single investigator (EACVI TTE certified). Liver stiffness (LS) was assessed by transient elastography (TE, Fibroscan®, Echosens) and share wave elastography (SWE; Hitachi Arietta V70). Reliable results were defined as median value of 10 valid measurements with an IQR/Med <30% and expressed in kPa. Control attenuation parameter (CAP) assessed by TE was used to quantify liver steatosis.

Results: 100 patients were evaluated, but 10 did not fulfilled the inclusion criteria. The final analysis included.

90 patients, with mean age of 56.6 ± 11.1 years (67.7% males), 70% with alcoholic etiology and 57.8% with compensated cirrhosis. LS could be evaluated in 83.3% of cases by TE and in 97.7% of patients by Hitachi SWE. According to the new criteria cirrhotic cardiomyopathy was diagnosed in 55/90 (61.1%) of patients: systolic dysfunction in 57.7% (reduced EF <50% in 3.3%) and diastolic dysfunction in 6.7% of cases.

The presence of systolic dysfunction with reduced contractility (EF≤50% and/or GLS<−18%) seems to correlate with LS as assessed by Hitachi SWE and liver steatosis (Figure).

Conclusion: According to the new criteria >60% of the cirrhotic patients were diagnosed with cirrhotic cardiomyopathy. LS assessed by Hitachi SWE and liver steatosis seems to correlate with reduced systolic contractility.

SAT175

Prevalence of cirrhotic cardiomyopathy according to the old and new diagnostic criteria

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Background and Aims: The prevalence and associated factors of cardiomyopathy in cirrhotics remains unknown. Recently published new multidisciplinary diagnostic criteria of cirrhotic cardiomyopathy (Izzy et al. Hepatology 2019 Nov 11.doi:10.1002/hep.31034) define systolic dysfunction of the left ventricle as ejection fraction (EF) ≤50% and/or global longitudinal strain (GLS) <−18 or >−22%,while the

	Systolic dysfunction with reduced contractility EF≤50% and/or GLS<-18% (n=13) (A)	No systolic dysfunction GLS between -18 and -22% (n=37) (B)	Systolic dysfunction with hyper-contractility GLS>-22% (n=39) (C)	All patients with systolic dysfunction (n=52) (D)	Diastolic dysfunction (n=6) (E)	p value
Age (years)	63±10.3	56.8±10.1	54.1±11.5	56.3±11.8	66.1±11.1	A vs C: **p= 0.0001** other p>0.25
Male (%)	n=10 (76.9%)	n=25 (67.5%)	n=25 (64.1%)	n=35 (67.3%)	n=4 (66.6%)	All comparisons n. s.
Alcoholic etiology (%)	n=7 (53.8%)	n=29 (78.3%)	n=26 (66.6%)	n=33 (63.4%)	n=4 (66.6%)	all comparisons n.s.
Child-Pugh -A -B+C	n=9(69.2%) n=4(30.8%)	n=19(51.3%) n=18(48.7%)	n=24(61.5%) n=15(38.5%)	n=33(63.4%) n=19(36.6%)	n=3 (50%) n=3 (50%)	all comparisons n.s.
MELD	9.9±3.3	10.6±4.1	11.1±4.5	10.8±4.2	11.3±3.8	all comparisons n.s.
BNP (pg/ml)	131 (46-225)	85 (8.8-2629)	105 (26.8-2208)	112 (26.8-2208)	166 (78.5-525)	all comparisons n.s.
LS by TE (kPa)	52.9±27.1	34.4±19.3	39.4±23.5	41.5±24.3	39.7±24.8	A vs B: p=0.07 Other n.s.
CAP by TE (dB/m)	313±57.7	251.5±58.1	247.3±59.1	263.9±64.8	215.8±45.6	A vs B: **p=0.004** A vs C: **p=0.002** A vs D: **p=0.02** Other n.s.
LS by Hitachi SWE (kPa)	11±0.54	14.6±6.8	15.3±4.6	14.7±4.6	12.4±4.5	A vs B: **p=0.007** A vs C: **p<0.0001** A vs D: **p=0.0001** Other n.s.
Cardiac output CO (L/min)	5.6±1.6	5.3±5	5.3±1.9	5.4±1.8	5.9±1	all comparisons n.s.

Figure: (abstract: SAT174)

	Old criteria	New criteria	Both old and new criteria	p value (old vs new criteria)
Systolic dysfunction	n=14 (15.5%)	n=52 (57.7%)	n=7 (7.7%)	<0.0001
Diastolic dysfunction	n=45 (50%)	n=6 (6.6%)	n=5 (5.5%)	<0.0001

Figure: (abstract: SAT175)

diastolic dysfunction is diagnosed when three of following conditions are present: average E/e'>14, peak tricuspid regurgitation velocity>2.8 m/s, septal e < 7cm/s, left atrial volume index >34 ml/m^2. According to the old criteria (first presented in 2005 during the World Congress of Gastroenterology) systolic dysfunction was defined as presence of EF<55% and/or blunted response on stress testing, while diastolic dysfunction was diagnosed when at least one of the following conditions was present: E/A < 1, isovolumetric relaxation time >80 ms and deceleration time >200 ms. Response to myocardial stress testing was not used in clinical practice because of widespread use of beta-blockers and reduced general condition of many patients. Our aim was to assess the prevalence of cirrhotic cardiomyopathy according to the old and new diagnostic criteria.

Method: Consecutive patients with liver cirrhosis without structural heart disease, HCC outside Milan criteria, presence of TIPS and with optimal acoustic echocardiography window were included. Conventional and speckle-tracking echocardiography (Vendor GE, EchoPAC PC software) were performed by a single investigator (EACVI TTE certified).

Results: We evaluated 100 patients, but 10 did not fulfilled the inclusion criteria. The final analysis included 90 patients with a mean age of 56.6 ± 11.1 years (67.7% males), 70% with alcoholic etiology, and 57.8% with compensated cirrhosis. According to the old criteria (without stress testing) cirrhotic cardiomyopathy was diagnosed in 55.5% of patients: systolic-15.5%;diastolic-50% of cases. According to the new criteria cirrhotic cardiomyopathy was diagnosed in 61.1% of patients: systolic dysfunction- 57.7%;diastolic dysfunction-6.6% (Figure). EF ≤50% was present in 3.3%, GLS <−18% in 13.3% and GLS >−22% in 43.3% of patients.

Conclusion: Prevalence of diastolic dysfunction is significantly lower according to the new criteria, while the prevalence of systolic dysfunction was higher. Further follow-up of patients with increased contractility and GLS>-22% is needed (pathological value only in cirrhotic patients).

SAT176

Diagnostic and prognostic role of presepsin in patients with cirrhosis and bacterial infection

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Background and Aims: Diagnosis of bacterial infection (BI) in cirrhosis is often difficult due to the low accuracy of the available biomarkers, which poorly correlate with prognosis. Presepsin (PSP), a 13 kDa molecule produced by monocytes phagocytic activity, has been recently introduced as a potential biomarker for early diagnosis of BI. The study aimed to prospectively evaluate PSP levels in cirrhotics with and without BI, its accuracy for the early diagnosis of BI in comparison with other commonly used biomarkers (C-reactive protein (CRP), procalcitonin) and its prognostic role in terms of 28-d mortality.

Method: All adults with cirrhosis admitted at Multivisceral Transplant Unit - Padua University Hospital between 03.2016-06.2019 were consecutively evaluated. For each patient, demographic features, clinical condition and occurrence of BI at hospitalization were evaluated. PSP was measured by Pathfast technique (Chemiluminescent enzyme immune-assay); its accuracy for the early diagnosis of BI was tested creating a ROC curve and comparing it with that of CRP and procalcitonin. Patients' outcome was assessed using competing risk analysis, and a multivariable analysis was performed to evaluate predictors of 28-d mortality.

Results: 278 cirrhotic patients (M/F 179/99, mean age 56 ± 11 years) for a total of 448 hospitalizations were evaluated. Mean ± SD PSP value in the whole cohort was 1620 ± 3014 pg/mL, with a correlation with severity of liver disease according to Child-Pugh score. PSP value was significantly higher in patients with BI (28.3%) than in patients without (2486 ± 4068 vs. 1277 ± 2399 pg/mL; p = 0.001). Sensitivity and specificity of PSP for diagnosis of BI was 0.66 (95%CI 0.57–0.74) and 0.63 (95%CI 0.57–0.68), respectively. The accuracy of PSP in diagnosing BI was lower than CRP (AUC-ROC 0.68 vs. 0.77; p = 0.002) but similar to procalcitonin (p = ns). Considering the whole cohort, age, ACLF, PSP (HR 2.37; 95%CI 1.29–4.34), but not CRP nor BI, were independent predictors of 28-d mortality.

Conclusion: PSP showed a suboptimal accuracy for the early diagnosis of BI in hospitalized cirrhotic patients but it was an independent predictor of short-term mortality, likely reflecting the importance of pro-inflammatory state as prognostic marker in cirrhosis.

SAT177

Reduced efficacy of norfloxacin prophylaxis to prevent spontaneous bacterial peritonitis over time: a systematic review and meta-analysis

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Background and Aims: Due to an increasing prevalence of multi-drug-resistant organisms (MDRO) in patients with liver cirrhosis, the efficacy of antibiotic prophylaxis to prevent spontaneous bacterial peritonitis (SBP) has been debated. Aim of this study was to assess changes in effectiveness of SBP prophylaxis over time.

Method: We searched PubMed, Embase and the Cochrane Central Register of Controlled Trials from database inception to May 2019 to identify randomized controlled trials of patients with liver cirrhosis that assessed SBP occurrence/recurrence during antibiotic prophylaxis with the common antibiotic agents. Network meta-analysis was performed pooling data with regard to incidence rate ratios (IRRs) of SBP, death or extra-peritoneal infections.

Results: Overall, 1626 patients in 12 RCTs were included. During primary prophylaxis, incidence rate of SBP and death in the norfloxacin treated patients was 0.117 and 0.438 per patient year, respectively, and IRRs of placebo vs. norfloxacin were significantly higher (IRR 5.35, 95% CI 1.99–14.38, p = 0.0009 for SBP and IRR 2.04, 95% CI 1.20–3.44, p = 0.008 for death). However, we observed a noticeably reduced efficacy of norfloxacin to prevent SBP over time

(p = 0.019). The reduction of efficacy was even more pronounced when analysing IRR of SBP for all quinolones (class-effect, p = 0.017). In secondary prophylaxis, the applied models showed trends, yet no overall significant differences between treatment designs due to the limited number of available studies.

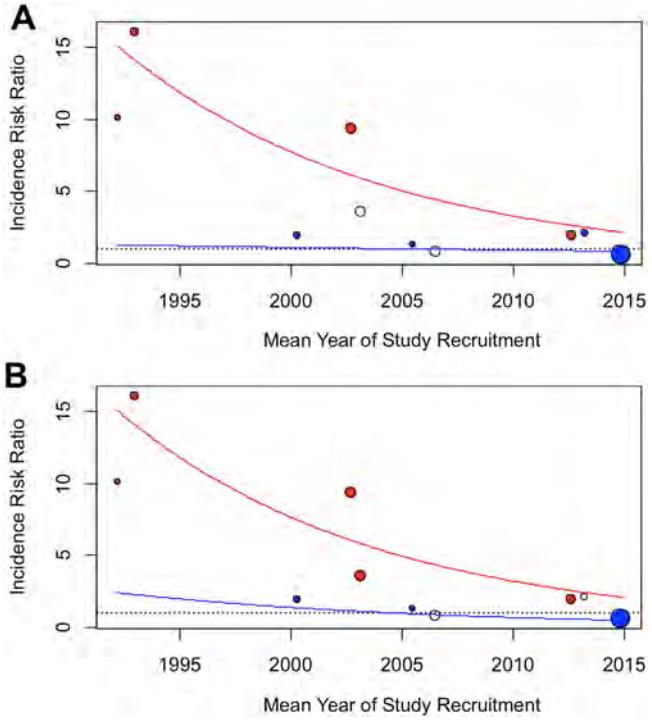

Figure: Meta-Regression plot of incidence rate ratios (IRRs) for spontaneous bacterial peritonitis. Panel A shows the results for norfloxacin, Panel B for fluoroquinolones in general. Red lines show the trend in decreasing IRRs for placebo vs. norfloxacin from direct and indirect comparisons and the blue line show the missing trend in other active treatments vs. norfloxacin from direct and indirect comparisons in a network meta regression model.

Conclusion: We observed a noticeably reduced efficacy of norfloxacin/quinolone for primary prophylaxis over time. Further studies to understand this phenomenon, e.g. the impact of colonization/infection with MDROs on prophylaxis, are urgently needed.

SAT178

Risk assessment of clinically significant portal hypertension by means of hepatosplenic volumetry in compensated cirrhosis

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Background and Aims: The presence of clinically significant portal hypertension (CSPH) defines the natural history of compensated cirrhosis (CC) and determines the treatment of patients with hepatocellular carcinoma (HCC). A recent study describes how different hepatic venous pressure gradient (HVPG) thresholds are associated with a progressive surgical risk. On the other hand, it has been suggested that visceral volumetry by computed tomography (CT) could estimate the degree of portal hypertension. **Aims:** 1) to compare the accuracy of CT-volumetry to predict CSPH with other non invasive methods (NIM): liver stiffness, platelets count, PSR (platelet-spleen ratio) and LSPS (liver stiffness to spleen/platelet score), 2) to evaluate the accuracy of CT-volumetry to predict CSPH in compensated patients with HCC.
Method: we included 223 patients with CC, CT and recent HVPG. The total liver volume (LV), the left to right volume ratio (LL/RL) and the spleen volume (SV) were calculated with Philips Intellispace® software. We used logistic regression techniques to build the predictive models and to assess de risk.
Results: 81.2% of the cases were men, 80.7% had HCC and in 70.1% the aetiology was viral (87.3% hepatitis C). The mean HVPG was 10.8 (5.1) mmHg and 52.7% presented HPCS. The mean liver stiffness was 20.1 (13.8) Kpa. The median time between CT and catheterization and elastography was 1.0 (IQR 0.5–2.2) and 1.1 (IQR 0.5–4.0) months, respectively. Both LL/RL and SV were independently related to CSPH (OR 7.1, p = 0.018 and OR 1.1, p = 0.000). The different AUCs to predict CSPH were 0.77 (95%CI 0.71–0.82) for LV, 0.71 (95%CI 0.64–0.77) for LL/RL and 0.81 (95%CI 0.75–0.86) for the multiplication LL/RLxSV. There were no differences in the AUCs to predict CSPH for LL/RLxSV and other NIM (LL/RLxSV 0.85 vs elastography 0.82, ns; LL/RLxSV 0.85 vs elastography and platelets 0.88, ns; LL/RLxSV 0.81 vs PSR 0.81, ns; and LL/RLxSV 0.85 vs LSPS 0.89, ns). In the subgroup of patients with HCC (n = 172), the AUC for LL/RLxSV reached 0.83 (95%CI 0.77–089). If we combine the cut-off points LL/RLxSV <79 cc (S 97.7%, E 31.4%) to discard CSPH and >359 cc (S 36.1%, E 97.7%) to confirm HPCS, up to 36.0% of the sample cases could be classified (2.3% false negatives and false positives).
Conclusion: CT-volumetry is a useful and accessible tool to predict CSPH, with a similar accuracy to other NIM. In compensated patients with HCC, a single CT scan would confirmed the diagnosis of HCC, determine the tumour stage and assess the risk of CSPH to select the patients that require catheterization.

SAT179

Zinc deficiency in cirrhosis predicts hepatic decompensation and mortality

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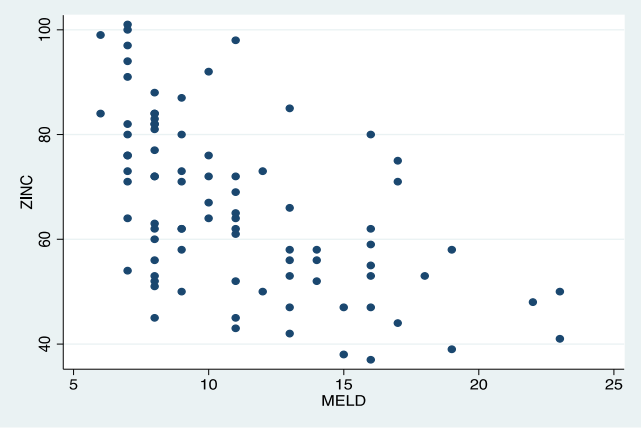
Background and Aims: Zinc is an important micronutrient that has been most evaluated and that has been associated with higher severity and worse prognosis in patients with liver cirrhosis.
Method: Prospective study in which all outpatients attending the cirrhosis care clinic were consecutively included. At the time of inclusion, it was performed: blood test, anthropometric measurements and bioimpedanciometry. The diagnosis of cirrhosis was based on the combination of clinical features, radiological images, presence of portal hypertension, compatible biochemical parameters and/or compatible biopsy findings. The exclusion criteria were: history of chronic respiratory or cardiovascular disease, chronic renal failure or hemodialysis, HIV coinfection, previous renal or hepatic transplantation, history of neoplasia requiring chemotherapy or radiotherapy, hepatocellular carcinoma outside of Milan criteria, intestinal resection, TIPs and lack of will to participate in the study.
Results: From 2016 through 2019, 329 patients were evaluated, of which 254 met all the inclusion criteria and none of the exclusion criteria. 56 patients (22.1%) presented zinc deficiency. In the multivariate analysis the factors that were independently associated with the presence of zinc deficiency were: alcoholic liver cirrhosis (OR 3.2, 95% CI 1.4–7.4; p = 0.007), higher Child -Pugh score (OR 1.3, 95% CI 1.1–1.5; p < 0.001) and lower phase angle (PA) by bioimpedanciometry (OR 0.3, 95% CI 0.2–0.5; p < 0.001). In our study we show a moderate correlation between zinc levels and the severity of liver disease measured by MELD score (r = –0.47; p < 0.001) (Figure). Regarding the prognostic implications, patients with zinc deficiency had a higher risk of liver decompensation (41.5 vs. 11.3%; p < 0.001),

including hepatic encephalopathy (18.9 vs. 2.6%; p < 0.001). They also presented a higher risk of mortality during follow-up (21.2 vs. 3.6%; p < 0.001).



Conclusion: Zinc deficiency is more frequent in patients with alcoholic liver cirrhosis, higher severity of liver disease and lower PA. In addition, the deficit of this micronutrient has prognostic implications, both in terms of liver decompensation and mortality. Furthermore, its correction with oral zinc supplementation is simple.

SAT180

A nomogram as an indirect method to identify sarcopenia in patients with liver cirrhosis

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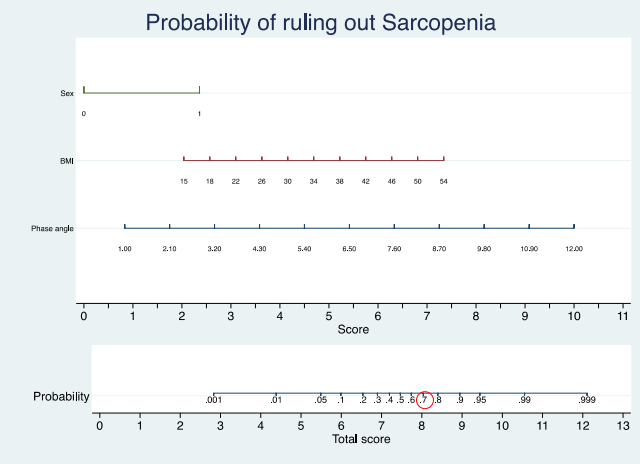
Background and Aims: Sarcopenia (loss of muscle mass) in liver cirrhosis has been associated with worse prognosis. Although CT scan is the gold standard for diagnosis of sarcopenia, it is necessary to find indirect methods to identify it.

Method: We performed a prospective study in which all outpatients with liver cirrhosis and recent CT scan evaluated at the cirrhosis care clinic were consecutively included. At the time of inclusion, it was performed: blood test, anthropometric measurements and bioelectrical impedance analysis. The diagnosis of cirrhosis was based on the combination of clinical features, radiological images, presence of portal hypertension, compatible biochemical parameters and/or compatible biopsy findings. The exclusion criteria were: carrying a cardiac pacemaker or metal implants, amputated limbs, chronic renal failure or hemodialysis, HIV coinfection, previous renal or liver transplantation, a history of neoplasia requiring chemotherapy or radiotherapy, hepatocellular carcinoma outside of Milan criteria and TIPs.

Results: 174 patients met all the inclusion criteria and none of the exclusion criteria. 71 patients (40.8%) had sarcopenia on CT scan. In the multivariate analysis, the factors that were independently associated with the presence of sarcopenia on CT scan were: male sex (OR 33.6 95% CI 8.8–128.3; p < 0.001), lower body mass index (BMI) (OR 1, 2 95% CI 1.1–1.4; p < 0.001) and lower phase angle (PA) by bioelectrical impedance analysis (OR 3.5 95% CI 2.0–5.9; p < 0.001). With the variables resulting from the multivariate study, we developed a nomogram (Figure) that would allow us to rule out the presence of sarcopenia. Our model rules out sarcopenia with an area under the receiver operating characteristic curve (AUROC) value of 0.88. The cut-off point of the probability to rule out sarcopenia was 0.70 (sensitivity 76%, specificity 84% and Youden index 0.60).



Conclusion: Sarcopenia is one of the most common complications of cirrhosis, associated with an increased risk of morbidity and mortality. Therefore, it is necessary to perform a properly nutritional evaluation in these patients. But since the CT scan has radiation exposure and limited availability, we propose using this nomogram as an indirect method to rule out sarcopenia in those patients in whom there is no clinical indication for CT scan.

SAT181

Impact of beta blocker therapy on systemic inflammation stratified by hepatic venous pressure gradient response

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Background and Aims: Non-selective beta-blockers (NSBB) decrease portal pressure, i.e. hepatic venous pressure gradient (HVPG) in patients with clinically significant portal hypertension. Interestingly, NSBB may also exert anti-inflammatory activity.

Method: We assessed markers of systemic inflammation (WBC, CRP, IL-6, PCT) and endothelial dysfunction (VWF) at sequential HVPG measurements, i.e. without NSBB at baseline (BL) and with NSBB at follow-up (FU). The impact of NSBB on these biomarkers was assessed by paired analyses stratified by Child-Turcotte-Pugh stage (CTP), type of NSBB, and HVPG-response (≥20% relative decrease/decrease to <12 mmHg).

Results: 332 patients were included: median age: 56 years; CTP-A = 94 (28.3%), B = 174 (52.4%), C = 64 (19.3%). Carvedilol and propranolol were used in 206 (62.0%) and 126 (38.0%) patients, respectively. HVPG-response was achieved in 111 patients (33.4%).

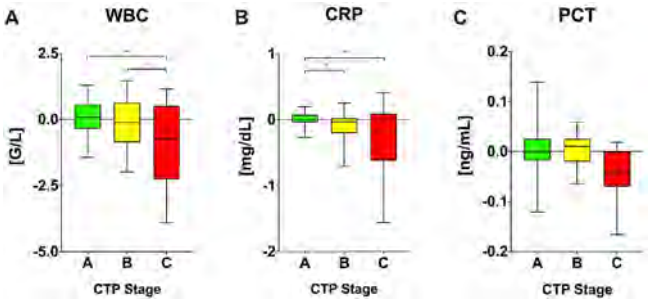
NSBB therapy was associated with a significant decrease of WBC (median: −1.8%; median 4.71 [IQR 3.12] to 4.60 [2.91] G/L; p = 0.021), and of CRP levels (−12.59%; 0.41 [0.81] to 0.33 [0.59] mg/dL; p < 0.001), while no significant effects were seen on IL-6 (10.79 [21.25] to 12.60 [14.39] pg/mL; p = 0.544) and PCT (0.12 [0.14] to 0.12 [0.10] ng/mL; p = 0.348). Moreover, VWF significantly decreased under NSBB therapy from 342 (163) to 306 (157)% (p < 0.001).

CTP-C patients showed most pronounced reductions in WBC (−14.58%; 5.74 [4.1] to 5.19 [2.74] G/L; p = 0.001), CRP (-24.88%; 1.15 [1.44] to 0.75 [1.19] mg/L; p = 0.003), and PCT levels (−16.67%; 0.20 [0.08] to 0.15 [0.07] ng/mL; p = 0.022); and their absolute changes in HVPG correlated significantly with changes in WBC (R = 0.306; p = 0.014).

Achieving an HVPG-response was associated with more significant decreases of WBC (−7.56%; 4.97 [3.2] to 4.62 [3.26] G/L vs. +0.71%; 4.45 [2.96] to 4.58 [2.84] G/L; p = 0.001) but similar decreases of CRP (−14.29%; 0.32 [1.18] to 0.28 [0.73] mg/dL vs. −12.68%; 0.42 [0.68] to 0.34 [0.46] mg/dL; p = 0.698) as compared to HVPG non-responders.

In contrast to propranolol, carvedilol led to pronounced decreases in WBC (−3.85%; 4.75 [2.96] to 4.39 [3.16] G/L vs. +2.92%; 4.67 [3.33] to 4.93 [2.76] G/L; p = 0.02), however, decreases of CRP were found with both treatments (−15.25%; 0.35 [0.69] to 0.28 [0.54] mg/dL vs. −3.45%; 0.5 [0.98] to 0.47 [0.71] mg/dL; p = 0.722).

Importantly, a NSBB-induced decrease of WBC by ≥15% was also associated with amelioration of systemic IL-6 (−24.51%; mean 23.89 ± 26.22 to 14.05 ± 11.52 pg/mL; p = 0.059) and PCT (−18.33%; 0.14 [0.13] to 0.12 [0.12] ng/mL; p = 0.017) levels.



Conclusion: NSBB therapy exerts systemic anti-inflammatory activity as suggested by decreases in WBC and CRP levels. This effect seems most pronounced in CTP-C, HVPG-responders and with carvedilol treatment. Moreover, NSBB treatment may ameliorate endothelial dysfunction.

SAT182

Protective effects of statin therapy in liver cirrhosis are limited by the common SLCO1B1 variant

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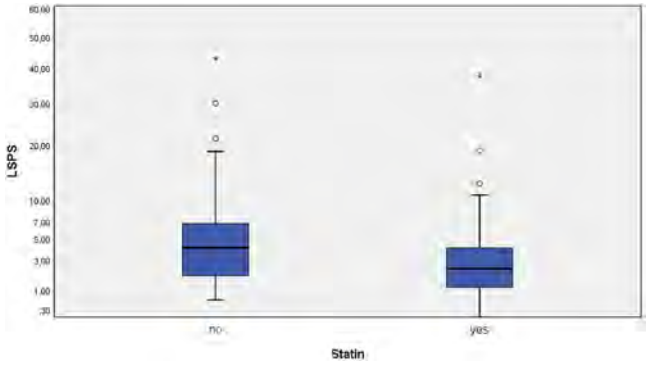
Background and Aims: Complications of liver cirrhosis and portal hypertension (PH) might be reduced by statin therapy. We aimed to assess whether this effect is reflected in the liver-stiffness to platelet score (LSPS), an important non-invasive marker of PH. The common loss-of-function variant p.A174 V in the transporter SLCO1B1 mediating the hepatic uptake of statins, results in decreased transporter function. The specific aim of this study was to assess the impact of statin therapy and to control confounders by propensity score matching (PSM) in a cohort of patients with cirrhosis, stratified for the genotypes of the *SLCO1B1* variant.

Method: In total, we identified 1,088 patients with liver cirrhosis in two German academic medical centers in Homburg and Halle. After exclusion and PSM, we included 154 patients on statins and 154 matched controls who never used statins. Complications of liver cirrhosis were retrospectively assessed applying EASL consensus criteria. The patients were genotyped for the common variant of *SLCO1B1* p.A174 V (rs4149056) using allelic discrimination assays.

Results: After PSM, standard deviation of all matching-parameters was reduced and the distribution of characteristics was equalized; genotype distribution was consistent with Hardy-Weinberg equilibrium. Concerning signs of PH, patients on statins presented less frequently with varices (OR 0.39; 95% CI 0.23–0.66; p < 0.001) and lower LSPS (4.8 ± 11.5 vs. 5.6 ± 6.4; p = 0.021). Decompensation events were significantly reduced in patients on statins (OR 0.54; 95% CI 0.32–0.90; p = 0.018). Ascites (OR 0.61; 95% CI 0.38–0.97; p = 0.038) and variceal bleeding (VB) (OR 0.35; 95% CI 0.15–0.83; p = 0.017) occurred less, whereas hepatorenal syndrome (HRS), jaundice and hepatic encephalopathy (HE) were distributed equally among the groups. Patients carrying at least one risk allele presented significantly more often varices (OR 2.68; 95% CI 1.24–5.81; p = 0.011) and HRS (OR 11.07; 95% CI 1.11–110, p = 0.011). In addition, bacterial infections (OR 2.5, 95% CI 1.14–5.47; p = 0.02), in particular spontaneous bacterial peritonitis (OR 3.47; 95% CI 1.16–10.38; p = 0.02), were more frequent in these patients.



Conclusion: In this PSM cohort, complications and signs of PH were markedly reduced in patients with liver cirrhosis treated with statins, as reflected by LSPS. This effect was diminished by the common mutation of the statin transporter *SLCO1B1*. Further prospective studies in independent cohorts are warranted to confirm these genotype-restricted observations.

SAT183

Shifting the focus of liver cirrhosis to prevention with the help of the SEAL program

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Background and Aims: Most patients with liver cirrhosis are detected at late stage of their disease. In approximately 75% of

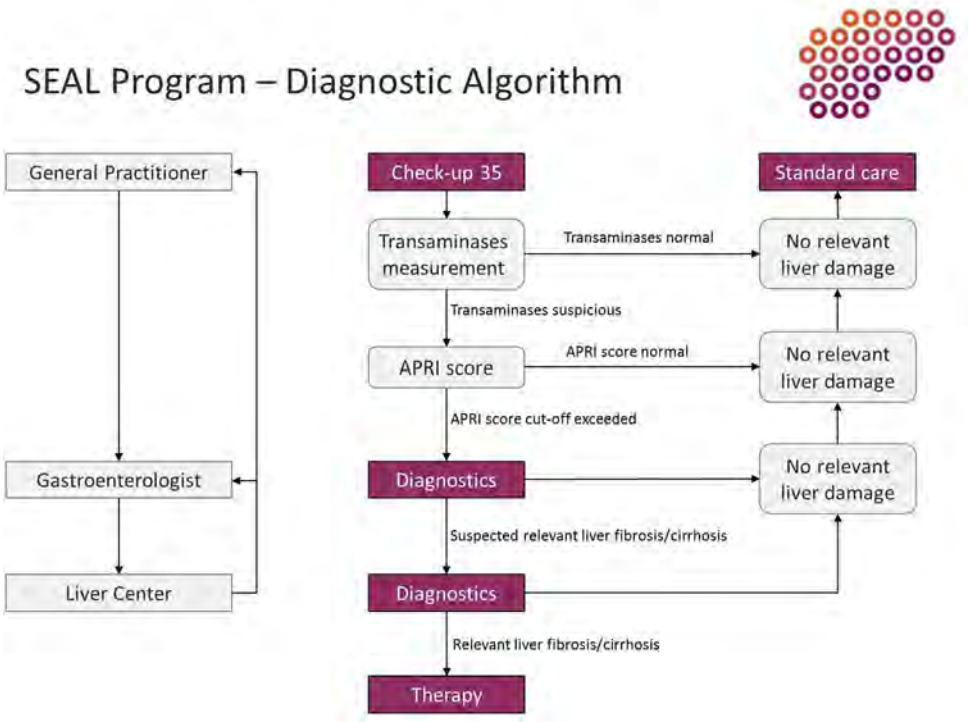

Figure: (abstract: SAT183)

these patients, diagnosis is based on the development of complications such as ascites or variceal bleeding. At this stage, causative treatment interventions are less successful or even impossible. Screening for liver health and disease is not included in standard medical check-up programs in Europe. The SEAL algorithm investigates the feasibility, effectiveness and cost-benefit assessment of a general screening strategy for liver fibrosis and cirrhosis in Germany.
Patients and Methods: As part of the SEAL program funded by the Federal Joint Committee (G-BA), 16,000 individuals are offered additional testing of liver enzymes by general practitioners as part of a nationwide primary care program (Check-up 35) in two federal states (Rhineland-Palatinate and Saarland). In case of elevated serum aminotransferase activities, the APRI score as liver fibrosis risk score is calculated. If the APRI score is suggestive for liver disease, patients are referred to a gastroenterologist for further differential diagnostic assessment. Patients with suspected liver fibrosis are referred to a tertiary liver center for full hepatologic work-up. Endpoints are cost-effectiveness of early diagnosis as well as data on the epidemiology of elevated liver enzymes and liver fibrosis in the general population.
Results: To date, 7.100 patients have been recruited. Of the examined patients, 11% and 6% presented with increased ALT and AST activities. Notwithstanding that in 499 patients a known liver disease was already present at inclusion, 11% of patients without known liver disease presented with elevated aminotransferases. Overall, 307 patients (4.3%) showed elevated ALT or AST and a conspicuous APRI score ≥0.5, 76% of whom were not known to suffer from chronic liver disease. Up to now, referral for further diagnostics was indicated in 245 patients.
Conclusions: To date, strategies to establish the diagnosis of chronic liver diseases as early as possible has been controversially discussed by physicians and health care providers. Our screening data indicate that a relevant group of the population is not aware of their increased aminotransferases or chronic liver diseases. The SEAL program provides novel data on the cost-effectiveness and utility of screening for liver diseases in Germany in particular and segmented health care systems in general.

SAT184

Algorithm to predict development of sarcopenia after transjugular intrahepatic portosystemic shunt in decompensated cirrhosis

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Background and Aims: Meticulous patient selection for treatment of portalhypertensive complications with transjugular intrahepatic portosystemic shunt (TIPS) is important for beneficial effects and sarcopenia has been reported as a risk factor for post-TIPS hepatic encephalopathy (HE) and mortality. This study evaluates the prognostic role and a predictive algorithm of post-TIPS sarcopenia.
Method: This study included patients with decompensated liver cirrhosis undergoing TIPS procedure from the prospective NEPTUN cohort. In a training cohort, CT scans before and after TIPS were analyzed to obtain transversal psoas muscle thickness (TPMT). In a validation cohort, CT scans after TIPS were analyzed for TPMT. Primary endpoint was mortality. Secondary endpoints were acute decompensations and acute-on-chronic liver failure (ACLF). A sequential muscle prediction (MP)-algorithm was developed.
Results: In the training cohort, 43 patients (23 female) were included. 13 patients were sarcopenic before TIPS. After TIPS 6 sarcopenic patients improved their muscle mass classified as non-sarcopenic, while 3 non-sarcopenic patients developed sarcopenia. Pre-TIPS sarcopenia was associated with post-TIPS HE. Post-TIPS sarcopenia was an independent predictor of 1-year mortality. Post-TIPS muscle loss was a predictor of development of ACLF and associated with higher mortality. Low pre-TIPS aspartate aminotransferase (AST) level and high CLIF-C AD score were associated with development of post-TIPS sarcopenia. MP-Algorithm predicted post-TIPS sarcopenia

in training and validation (n = 105) cohort with an accuracy of 91% and 80%.
Conclusion: This study demonstrates that post-TIPS muscle loss predicts ACLF and death in decompensated cirrhotic patients receiving TIPS and offers an easy-to-obtain MP-algorithm to predict development of post-TIPS sarcopenia.

SAT185
In-hospital falls and fall-related injury in patients with liver-cirrhosis - malnutrition matters
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Background and Aims: Patients with liver cirrhosis are prone to develop complications such as complicated infections and renal failure. Particularly malnutrition in patients with cirrhosis is associated with higher rates of mortality and morbidity. Here, we aimed at assessing the actual risk of falling and defining risk factors that can help prevent and create awareness towards falls of hospitalized patients with liver cirrhosis.
Method: In a retrospective analysis, hospitalized patients with liver cirrhosis from 2014 to 2019 at University Hospital Frankfurt were characterized and patients with documented falls further assessed for risk factors. Falls were documented in a standardized clinic-wide form in the patient's electronic file, from which clinical data was collected.
Results: In total, 5830 hospitalizations of 2553 patients with liver cirrhosis were included in the study. Patients were predominantly male 67.6% (3941/5830). Median age was 60 years. A total of 251 (4.3%) falls by 206 patients (3.5%) were documented in this cohort in the analyzed time frame; median age in this group was 64 years.
Out of 206 patients with described falls, 127 (61%) had alcoholic liver cirrhosis, 54 (26.1%) viral cause (HBV 24; HCV 30). Most common cause for admission in patients who fell were hydropic decompensation (91/206) and hepatic encephalopathy (62/206). Falls were mostly described as a slip to the ground (93/251), 47 (18%) patients fell on their way to the bathroom. Major injuries (fractures, bleedings, associated death) were observed after 14 (5.6%) falls, minor injuries (hematoma, pain or scratches) were seen in 96 (38.25%) falls, while 147 (58.57%) falls were not followed by any injury. Malnutrition was assessed via the nutritional risk screening (NRS). According to the NRS 60 of 168 cases (35.7%) had a risk score >1, indicating a moderate to severe impaired nutritional status. A NRS score >1 was significantly correlated with fall related injury ($p = 0.015$); Both, male gender ($p = 0.005$; OR 2.837) and malnutrition ($p = 0.01$, OR 2.579) were independently associated with fall related injury in the multivariate model.
Conclusion: Falling patients with cirrhosis are at high risk for moderate to severe injuries. Malnutrition proved to be an independent risk factor in the fall assessment of patients with liver cirrhosis, thus, warranting its assessment and counteraction.

SAT186
Body composition parameters predict outcomes of acute kidney injury in patients with cirrhosis
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Background and Aims: Sarcopenia and adipopenia influence prognosis in cirrhosis. We examined whether body composition markers of adipose and muscle tissue associated with renal function and clinical outcomes in cirrhotic in-patients after a first episode of acute kidney injury (AKI).
Method: In a single-center retrospective cohort study, we identified 73 cirrhotic patients with a first episode of AKI and computed tomography (CT) within 12 weeks of AKI followed for 6 months or until death/transplantation. CT images collected at the level of third lumbar (L3) vertebra were used to assess body composition parameters, including adipose tissue indices normalized to height in cm^2/m^2 (subcutaneous - SATI, visceral - VATI, intramuscular - IMATI, total - TATI), the L3 skeletal muscle index (SMI), and mean tissue densities in HU. Sarcopenia was defined according to guidelines as an SMI < 50 cm^2/m^2 in men and < 39 cm^2/m^2 in women.
Results: Forty-three (59%) patients were male; mean age was 60.0 ± 10.3 years. The prevalence of sarcopenia in men and women was 70% and 73%, respectively ($p = 0.80$). Mean follow-up was 21.2 ± 20.5 months. Absence of sarcopenia was associated with resolution of AKI at day seven (D7) (OR 5.56, $p = 0.004$). SMI correlated with estimations of renal function at D7 as calculated by MDRD6-eGFR ($r = 0.31$, $p = 0.01$), CKDEPI-eGFR ($r = 0.31$, $p = 0.01$) and RFH-eGFR ($r = 0.27$, $p = 0.02$), but not with creatinine ($r = -0.05$, $p = 0.66$). Among adipose tissue parameters, SATI was associated with AKI resolution at D7 (OR 1.02, $p = 0.02$). High IMATI was associated with 90-day mortality/transplantation (OR 1.32, $p = 0.025$). Higher mean density of SAT and VAT (OR 1.05, $p = 0.009$, and OR 1.1, $p = 0.007$) were associated with 90-day mortality and transplantation. In univariate analysis, high SAT density was associated with progression of AKI at D7 (OR 1.05, $p = 0.038$).
Conclusion: Higher SMI and SATI – reflecting more preserved muscle and adipose tissue mass - were associated with favorable evolution of renal function in cirrhotic patients following an AKI episode. High IMATI was associated with 90-day mortality/survival. High SAT density - possibly indicating subcutaneous adipose tissue edema or inflammation - was associated with progression of renal failure as well as mortality and transplantation.

SAT187
Usefulness of handgrip as a non-invasive tool to predict the outcome of patients with cirrhosis. A prospective study
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Background and Aims: Malnutrition is an independent predictive factor of mortality and morbidity in patients with cirrhosis. Recently, handgrip (HG) emerged, in cirrhotic male patients only, as a better predictor of mortality compared to other invasive techniques (1). We aimed to confirm the effectiveness of HG as a mortality predictor in patients with cirrhosis and to compare it to other non-invasive indicators of malnutrition.
Method: Observational, prospective study including all cirrhotic patients admitted to a tertiary Belgian center from January 2017 to August 2018. Non-invasive malnutrition evaluation was based on HG (2), Mid Arm Circumference (MAC) and Subjective Global Assessment (SGA, 3). HG <20 Kg in female and <30 kg in male were used to identify patients at risk of malnutrition ("Risk HG" group). Chi Square or Fisher Test were used to compare outcomes and variables, Kaplan Meier (Log Rank test) to estimate the cumulative survival and Cox Regression to model predictors of overall and 90-day mortality ($p < 0.05$). Transplanted patients were censored for the survival analysis.
Results: Eighty-nine cirrhotic patients were included: male 62 (69.7%), age 59.8 (±10.4), MELD 15 (IQR 9). Among them, 63 patients (70.8%) had alcohol related cirrhosis, 47 were admitted for an acute decompensation (52.8%), 19 presented HCC (21.3%) and 33 underwent liver transplantation (37.1%). The median follow-up was 161

days (IQR 258), and, during the observation period, 15 patients (16.9%) died, 11 within the 90th day. The estimated overall and 90-day survival rates were inferior for patients belonging to the "Risk HG" group (64.4% vs 83.4%, p = 0.033 and 93.0% vs 75.0%, p = 0.028, respectively, Fig. 1). On the other hand, increased mortality was not detected according to SGA and MAC. Predictors of overall and 90-day mortality at the univariate analysis were BMI (OR 1.12, p = 0.029 and HR 1.19, p = 0.007 respectively), MELD score ≥17 (OR 2.96, p = 0.040 and HR 3.33, p = 0.055 respectively), "Risk HG" (OR 3.1, p = 0.043 and HR 4.07, p = 0.042 respectively) and albumin (OR 0.92, p = 0.040 and HR 0.87, p = 0.04 respectively). The multivariate analysis confirmed, for both overall and 90-day outcome, the "Risk HG" (OR 3.1, p = 0.042 and HR 4.3, p = 0.035) as the only predictor of poor survival.
Conclusion: This study confirms, in a heterogeneous population of cirrhotic patients, that low HG is associated with worst survival, while other non-invasive methods of malnutrition assessment failed. These results should be validated in larger cohorts in order to support the integration of HG to MELD score as a tool for predicting mortality in cirrhotic patients.

References

1. Sinclair M et al., *Liver Transpl* 2019.
2. Giusto M et al., *Eur J Gastroenterol Hepatol* 2015.
3. Detsky AS et al., *JPEN* 1987.

SAT188

Longitudinal assessment of progressive decrease in platelet counts as a surrogate marker of liver fibrosis and portal hypertension

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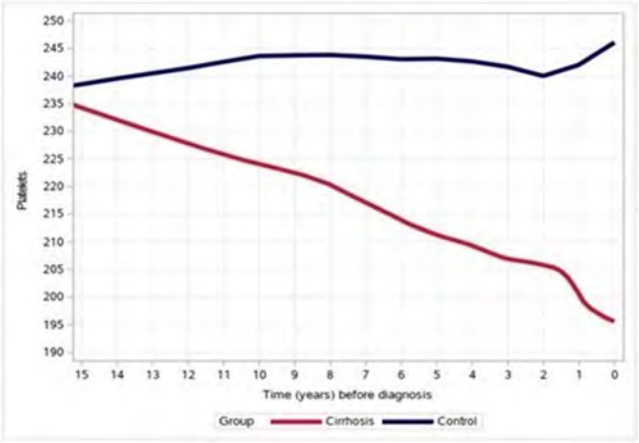
Background and Aims: Most non-invasive scores predicting hepatic fibrosis incorporate platelets as a strong risk factor which is incorporated in the formula as a single point measurement. However, little is known about the association between longitudinal changes in platelets count (PTC), when still within the normal range, and the risk of cirrhosis. Our aim was to explore whether PTC trajectories over time can predict the diagnosis of liver disease across the different aetiologies and complications of cirrhosis and portal hypertension, assessing their gradual effect on various fibrosis scores respectively.
Method: A nested case-control study utilizing a computerized database of a national payer-provider insurer. Cirrhosis cases (n = 5258) from 2001 to 2018 were compared to controls (n = 15,744) matched for age, sex at a ratio of 3:1. All participants had multiple laboratory measurements prior to enrolment and trends throughout the preceding 20 years were calculated. The association between PTC, cirrhosis complications and fibrosis scores prior to cirrhosis diagnosis was investigated, compared to healthy controls. Liver enzymes and synthetic liver tests were evaluated correspondingly.
Results: The leading aetiologies were viral infection, alcoholic liver disease and NAFLD. The mean PTC decreased from 235,000/μL to 190,000/μL up to 15 years prior to cirrhosis diagnosis compared to controls whose PTC remained stable. This trend was consistent regardless of sex, cirrhosis etiology and was pronounced in patients who developed complications of portal hypertension mainly varices and ascites. AST and ALT increased from 40 to 75 U/l, bilirubin increased gradually from 0.6–1.2 mg/dL and albumin decreased mildly from 4.5–3.8 mg/dL compared to controls. In concordance to the gradual PTC decrease and AST and ALT increase, FIB-4 increased gradually ranging from 1.3 to 3 prior to cirrhosis diagnosis. In multivariable regression analysis, a decrease of 50 units in PTC was associated with 1.3 times odds of cirrhosis (95%CI 1.25–1.35).



Conclusion: In the preceding years before the diagnosis of cirrhosis, there is a progressive decline in average PTC occurs, within the normal limits, matched to a gradual increase in fibrosis scores. This should alert the treating physicians of an early liver disease and may serve as a non-invasive tool for early diagnosis.

SAT189

Factor VIII/protein C and not ADAMTS13/VWF:Ag ratio is a prognostic risk factor for patients with cirrhosis and low MELD score

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Background and Aims: The pro-hemostatic imbalance of cirrhosis has been postulated as one of the mechanisms explaining liver damage. Low ADAMTS13/Von Willebrand Factor antigen (VWF:Ag) and high factor VIII/protein C ratio (FVIII/PC) represent biochemical markers of platelet hyperaggregation (primary hemostasis) and hypercoagulation (secondary hemostasis), respectively. This study describes the association of such hemostatic parameters with the severity of the liver disease measured by Child-Pugh, MELD, MELD-Na and their prognostic role on the clinical outcome.
Method: We investigated 123 patients (78% male, age 62 ± 12, 58% in-hospital) with cirrhosis Child-Pugh:8.2 ± 2.2, MELD:15.6 ± 7.7, MELD-Na:16.3 ± 6.6. The main etiologies were virus (40%), alcohol (30%), virus + alcohol (15%). The hemostatic parameters included: VWF:Ag, ADAMTS13 activity, the pro-(FVIII, FII)and anti-coagulant factors (antithrombin, PC). Their correlations with indexes of severity were tested by the Pearson coefficient. Patients were followed up to 12 months. Decompensation (requiring hospitalization), death or transplantation were retrospectively collected and presented as cumulative risk. The prognostic role of the hemostatic parameters was tested by logistic regression and finally expressed as risk of adverse outcome predicted by the model.
Results: Patients presented a pro-hemostatic imbalance resumed by ADAMTS13/VWF:Ag of 0.21+/−0.14 and FVIII/PC of 6.0 ± 6.5. All the hemostatic parameters correlated with all the markers of cirrhosis severity (p < 0.05). Adverse outcomes occurred in 74 patients: 35

(28%)decompensations, 23 (19%)deaths, 16 (13%) transplantations. MELD-Na had the highest prognostic accuracy (AUC = 0.809) in comparison with MELD (AUC = 0.774) and Child-Pugh (AUC = 0.771). Among all the hemostatic parameters, FVIII/PC was the only variable associated with the composite clinical end-point at logistic regression analysis (OR:1.215;95%-CI:1.05–1.38; p = 0.006). A prognostic model which included MELD-Na and FVIII/PC led to a slight increase of the AUC vs MELD-Na alone (AUC 0.815 vs 0.809) in the whole series. A FVIII/PC≥2.78 (i.e. the lowest tertile in our series) identified patients at higher risk of adverse outcome and was more evident in MELD-Na<15 (45% vs 27%) than in those with MELD-Na≥15 (83% vs 75%).
Conclusion: Markers of primary and secondary hemostasis correlate with common indexes of liver disease severity. FVIII/PC ratio has a relevant prognostic role in patients with MELD-Na<15.

SAT190

Baveno VI criteria as a prognosis index for clinical complications in patients with cirrhosis

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Background and Aims: The Baveno VI recommendations stated that the combination of liver stiffness measurement (LSM) and blood platelets could safely rule out varices needing treatment (VNT) in patients (pts) with compensated advanced chronic liver disease (cACLD). Upper endoscopy is not necessary in low-risk pts defined by a LSM <20 kPa and a platelet count >150 G/L. Few data are available regarding prognosis and liver-related complications in low-risk patients. We aimed to evaluate 4-year liver-related complications and survival in these patients.
Method: a retrospective analysis of prospectively collected data in a tertiary centre of Hepatology. All consecutive pts evaluated between 2012 and 2015 were analysed. Inclusion criteria were: 1) Cirrhosis (LSM≥12.5 kPa); 2) Absence of previous complication (i.e. ascites, hepatic encephalopathy (HE), variceal bleeding (VB), portal vein thrombosis or hepatocellular carcinoma (HCC)). Pts were divided into 2 groups: pts at low risk according to Baveno VI criteria (LSM <20 kPa and platelet count>150 G/L (Baveno VI favourable status)) and pts at high-risk (LSM ≥20 kPa or platelet count ≤150 G/L (Baveno VI unfavourable status)).
Results: 454 pts with cACLD were analysed (mean age 57 ± 11 yrs, male gender 72%, cause of cirrhosis hepatitis C/NASH/alcohol/hepatitis B/other in 42/25/17/10/6% of cases, Child-Pugh score A 100%, LSM 21,5 ± 11 kPa, platelet count 173 ± 74 G/L, VNT 19.6%). Two hundred and one patients had a favourable Baveno VI status, 1.35% with VNT. Mean follow-up was 3.6 ± 1.3 years. The 4-year probability of being free of developing ascites (96.2 vs 90.5%, p = 0.03), HE (99.4 vs 95.7%, p = 0.03), VB (99.4 vs 96.3, p = 0.05) or any hepatic decompensation (96 ± 1,5% vs. 89% ± 2,3%, p = 0.01) was higher in patients with Baveno VI favourable status. Overall, 28 pts developed hepatic decompensation. Baveno VI status was evaluated in 26 pts at the time of decompensation: all of them had an unfavourable status. The probability of developing HCC was significantly lower in pts with Baveno VI favourable status (3.9% vs 10.2%, p = 0.04). Liver-related mortality was no different between the 2 groups (p = 0.31). In Multivariate analysis, the independent factors associated with further development of hepatic decompensation were albumin (p < 0.001), bilirubin (p = 0.003), prothrombin time (p = 0.01) and LSM (p = 0.01).
Conclusion: In our series of pts with cirrhosis with Baveno VI favourable status, the 4-year probability of developing portal hypertension-related complication or HCC was significantly lower, compared to pts with unfavourable status. The Baveno VI criteria could predict clinical outcome in cACLD. As previously described, HCC has to be screened in this population.

SAT191

Systemic and splanchnic hemodynamic features of patients with porto-sinusoidal disease as compared with cirrhosis

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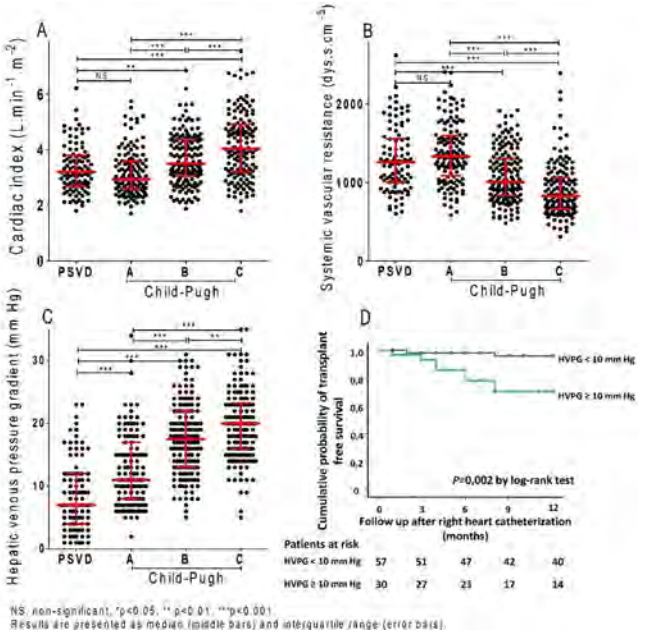
Background and Aims: Data on hemodynamic features of patients with porto-sinusoidal vascular disease (PSVD) are limited. We aimed at comparing systemic and splanchnic hemodynamic features of patients with PSVD with those of patients with cirrhosis.
Method: This retrospective study included all patients with signs of portal hypertension, who underwent liver and right heart catheterization at our center between 2011 and 2018 and had either of the 2 following conditions: (a) PSVD according to VALDIG criteria; (b) histologically proven cirrhosis related to alcohol consumption, chronic viral hepatitis, autoimmune hepatitis and/or metabolic syndrome. Non-inclusion criteria included infection or alcoholic hepatitis within 2 weeks before hemodynamic study. Biopsies were reviewed by an expert pathologist and histological elementary lesions were classified according to pre-specified criteria.



Results: We included 428 patients with cirrhosis (73% male, median age 57 years, 73% esophageal varices, 51% ascites) and 96 patients with PSVD (57% male, median age 59 years, 58% esophageal varices, 25% ascites). 77 (81%) patients with PSVD had at least one extra-hepatic condition known to be associated with PSVD. Cardiac index and systemic vascular resistance of patients with PSVD were similar to those of patients with Child-Pugh A cirrhosis, but patients with PSVD had lower cardiac index and higher systemic vascular resistance

than Child-Pugh B or C cirrhosis (Fig. A and B). Patients with PSVD had lower hepatic venous pressure gradient (HVPG) than patients with cirrhosis, whatever Child-Pugh score (Fig. C). Analyses restricted to patients without ascites or without betablockers gave similar results. Prevalence of portopulmonary hypertension was similar in PSVD (3%) and cirrhosis (2%) ($p = 0.401$). Ascites was more common among PSVD patients with HVPG ≥10 mm Hg than in those with HVPG <10 mm Hg (41% vs. 15% respectively, $p = 0.01$). Histological features associated with HVPG ≥10 mm Hg included portal vein narrowing ($p = 0.002$) and nodular regenerative hyperplasia ($p < 0.001$). After a median follow-up of 13 months, patients with PSVD and HVPG ≥10 mm Hg had lower transplant free survival than those with a lower HVPG (Fig. D).

Conclusion: Patients with PSVD had systemic hemodynamic features similar to those of patients with Child-Pugh A cirrhosis, but lower HVPG. Prevalence of portopulmonary hypertension was low and similar in PSVD and cirrhosis. HVPG ≥10 mm Hg was associated with a lower transplant free survival in patients with PSVD.

SAT192

Circulating microfibrillar-associated protein 4 is an independent predictor of transplant-free survival in compensated and decompensated cirrhosis

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Background and Aims: Circulating microfibrillar-associated protein 4 (cMFAP4) has been associated with advanced fibrosis in early stage liver disease related to alcohol and viral hepatitis C. We aimed to investigate cMFAP4 as a prognostic marker of transplant-free survival in patients with compensated and decompensated cirrhosis.

Method: We prospectively enrolled patients with compensated and decompensated cirrhosis from two Danish and one German hospital. Compensated patients were enrolled in relation to liver biopsy and only patients with verified cirrhosis were enrolled. Decompensated patients were enrolled in relation to therapeutic paracentesis. Patients were followed for up to 12 months, death or liver transplantation (LTx). cMFAP4 was compared to established prognostic models including Model for End-stage Liver Disease-sodium (MELD-Na), Child-Pugh Score (CPS) and CLIF Consortium Acute Decompensation score (CLIF-C AD). We used the median cMFAP4 (81.9 U/l) to divide the cohort into low-cMFAP4 and high-cMFAP4.

Results: We included 104 patients of which 45 were compensated and 59 were decompensated. Median age was 59 ± 8.2 years, 73% were male and 96 had alcohol-related cirrhosis. The median level of cMFAP4 was 123.6 U/l (95.3–162.6) in high-cMFAP4 and 49.1 U/l (31.1–69.2) in low-cMFAP4.

The distribution of Child-Pugh class (A/B/C) was 31/47/16 with more severe stages of disease in the group of low-cMFAP4 ($p < 0.01$). The median MELD-Na score was 16 (11–20), CLIF-C AD 52 (46–56) both significantly higher in the low-cMFAP4 group (OR = 0.88, $p < 0.01$; OR = 0.94, $p = 0.02$ respectively). During 12 months follow-up we observed 13 deaths (12.5%) and two LTx (1.9%). Transplant-free survival was significantly decreased in low-cMFAP4 compared to high-cMFAP4 ($p < 0.01$) (see Figure). In multivariate Cox regression with age, sex and MELD-Na as control variables high-cMFAP4 was independently associated with transplant-free survival (HR = 0.22, $p = 0.02$). An AUROC model comparing cMFAP4, MELD-Na, CPS, CLIF-C AD showed similar prognostic performance between the models. However, the highest AUROC was obtained in a combined model of CPS and cMFAP4 (AUROC = 0.65).

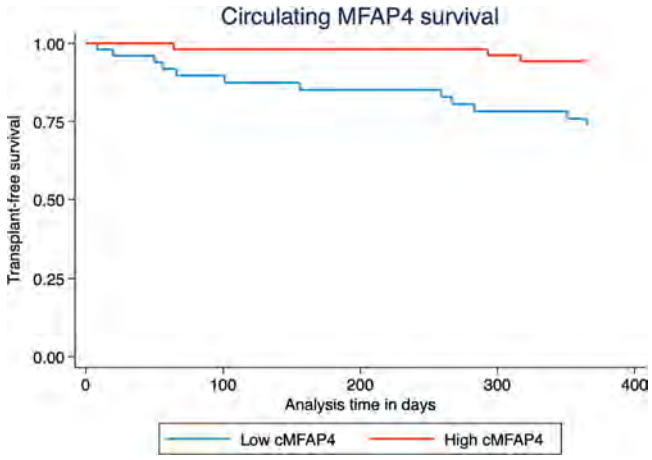

Figure: Kaplan-Meier curve of transplant-free survival.

Conclusion: Transplant-free survival was significantly lower in patients with lower levels of cMFAP4 independent of established prognostic biomarkers of mortality in cirrhosis. cMFAP4 is a strong independent predictor of transplant-free survival and adding this marker can be used to increase prognostic performance.

SAT193

Tunnelated peritoneal catheter versus large volume paracentesis for refractory ascites in cirrhosis: a randomized controlled trial

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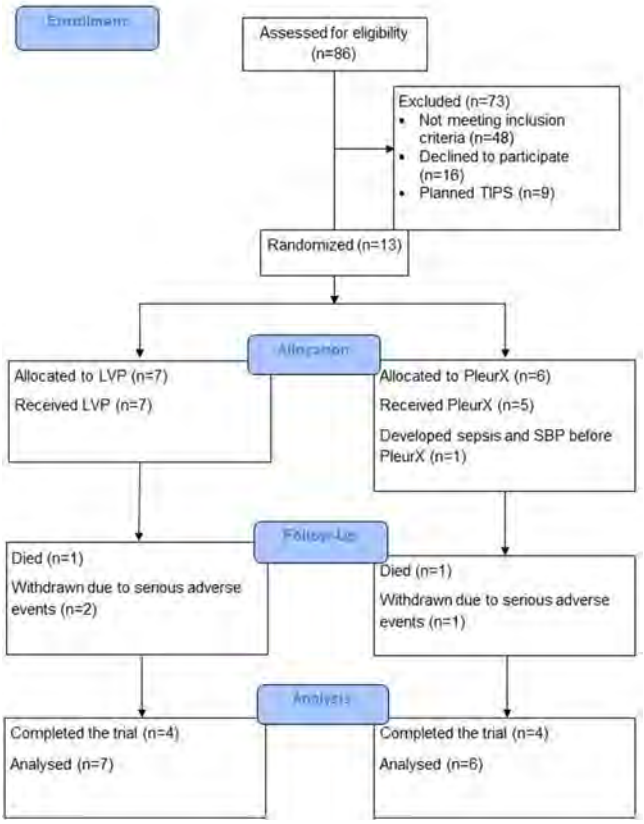
Background and Aims: Refractory ascites is associated with a median survival of six months. Repeated large volume paracentesis (LVP) and albumin infusion is standard treatment, but complications are common and involve hyponatriemia, bacterial peritonitis and renal impairment. The PleurX catheter is a tunnelated catheter with a cuff that allows entrenchment in the subcutaneous fat. Ascetic fluid is drained intermittently at the patient's home using vacuum containers. In a randomized controlled trial, we aimed to evaluate the beneficial and harmful effects of the PleurX catheter versus LVP and albumin infusion in patients with cirrhosis and non-malignant ascites.

Method: The trial was approved by relevant authorities (EudraCT: CIV-16-10-017324, H-16040179) and registered at clinicaltrials.gov (NCT03017635). Random allocation was computer-generated, and allocation was concealed using sealed opaque envelopes. Patients were included from January 2017 to December 2018. Inclusion criteria were I) adults with cirrhosis and recurrent ascites, II) expected survival of >3 months. Exclusion criteria were I) eligible

for TIPS insertion, II) hepatic encephalopathy or variceal bleeding within two weeks, III) ongoing infection, III) intraabdominal surgery within four months, IV) increased risk of complications as judged by the primary healthcare provider. Patients were monitored for infections and all culture positive samples were repeated after 14 days for verification.



Results: The study aimed to enrol 32 participants, but due to slow recruitment and implementation of the procedure at hospital departments, the trial was terminated prematurely after 13 patients allocated to PleurX (n = 6) versus LVP (n = 7). Seven were female, age range 51 to 80 years. No procedure related complications were observed. Two patients died within the first month. One died due to variceal bleeding (PleurX group). One died due to septicaemia of unknown origin and hepatorenal syndrome (HRS) (LVP group). One patient in the PleurX group was withdrawn before insertion of the catheter due to sepsis and HRS. One patient in the PleurX group was withdrawn after one month due to hyponatremia. In the LVP group, two patients were withdrawn due to SBP and HRS (n = 1) or infection of unknown origin (n = 1). In the PleurX group, all patients developed colonisation of the catheter within one to four months, but only two developed SBP. The most common bacterial colonisation was *Staphyloccous Epidermidis* (n = 4). In the LVP group, one participant developed SBP.

Conclusion: In selected patients, the PleurX catheter may be a safe alternative to LVP and efficiently mobilizes ascetic fluid, but the risk of infection should be considered in each case. The impact of colonization on the risk of infections including SBP as well as immunological dysfunction in cirrhosis needs further investigations.

SAT196

Efficacy of transjugular intrahepatic porto-systemic shunt in cirrhotic patients with hepatorenal syndrome - chronic kidney disease

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Background and Aims: transjugular intrahepatic porto-systemic shunt (TIPS) has proved to ameliorate renal function in patients with type 2 hepatorenal syndrome (HRS). However, available evidence is based on: 1- 'old' diagnostic criteria for type 2 HRS and not on the current definition of HRS–chronic kidney disease (CKD) and 2- studies of relatively small sample size. Among patients who underwent TIPS for refractory ascites over the last 11 years, we aimed to investigate the renal function of those with HRS-CKD.
Method: 38 out of 199 patients fulfilled the current diagnostic criteria for HRS-CKD and were included in the analysis. Renal function (serum creatinine - sCr and Glomerular Filtration Rate – GFR using Modification of Diet in Renal Disease 4 – MDRD4 and Chronic Kidney Disease Epidemiology Collaboration– CKD-EPI formulas) was evaluated 1 week and 1–3–6 and 12 months after TIPS.
Results: Renal function significantly improved since 1 week after TIPS (sCr: 1.94 ± 0.56 vs 1.40 ± 0.32 mg/dl; $p < 0.001$; GFR-MDRD4: 36.29 ± 9.65 vs 53.72 ± 14.4 ml/min/1.73 m2; $p < 0.001$), and the improvement was maintained during the follow up. Considering the baseline CKD stages, the amelioration in renal function was observed in stage G3a (GFR-MDRD4 49.81 ± 3.65 vs 59.31 ± 11.0 ml/min/1.73 m2; $p = 0.025$) as well as in stage G3b (GFR-MDRD4 38.29 ± 4.97 vs 53.75 ± 16.83 ml/min/1.73 m2; $p < 0.001$) and stages G4-G5 (GFR-MDRD4 25.25 ± 3.15 vs 50.43 ± 11.67 ml/min/1.73 m2; $p < 0.001$). Since one week after TIPS and during the whole follow up, sCr and GFR became comparable between stages G3a vs G3b vs G4-G5 ($p = ns$), whilst significantly different ($p < 0.05$) at baseline.
Conclusion: TIPS led to an early and persistent improvement in renal function in patients with HRS-CKD, irrespective of the baseline CKD stage. After TIPS, renal function parameters became rapidly comparable between patients with slightly reduced GFR and patients with severe HRS-CKD.

SAT197

The prevalence of esophageal varices needing treatment depends on gender, etiology and BMI

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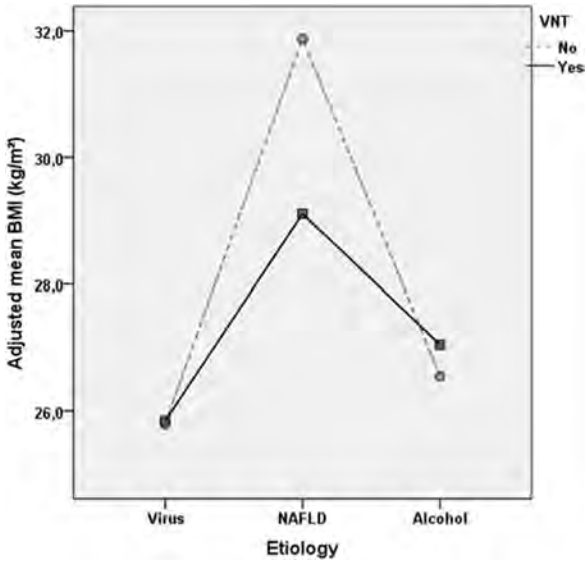
Background and Aims: The epidemiology of esophageal varices has so far been evaluated under conditions restricted by the size and etiology of the population. It is essential to know the epidemiological predictors to improve predictive scores. The main objective was to evaluate the epidemiology of varices needing treatment (VNT) in a vast population of multiple etiologies.

Method: 2,290 patients with chronic liver disease were included in 8 countries in a retro-prospective study. Their characteristics were, age: 59 ± 11 years, men: 63.5%, etiologies: virus: 50.0%, NAFLD: 29.5%, alcohol: 20.5%, BMI: 28.4 ± 5.8 kg/m², MELD score: 9.5 ± 3.0, liver stiffness ≥10 kPa: 93%. The VNT prevalence was 14.9%.
Results: The main significant differences between patients with VNT vs no VNT were: increased prevalence in men, high MELD, alcohol etiology and decreased in NAFLD vs virus etiology, lower BMI and creatinine. Thus, the odds ratio of VNT for men was 1.55 (1.19–2.03) after adjusting for covariates.
In multivariate analysis, the independent predictors of VNT were: etiology, sex, platelets, prothrombin index, liver stiffness, albumin and ALT without role for age, BMI, AST, creatinine, and MELD score. This model provided a first score of usual tests (SCOUT 1). A second model taking into account the multiple interactions called SCOUT 2 made it possible to increase the AUROC for VNT to 0.819 vs 0.806 for SCOUT 1 (p = 0.019). SCOUT scores were compared to published VNT scores ANTICIPATE and PLER (ratio platelets/liver stiffness). SCOUT 2 was very well calibrated according to gender, etiology and MELD unlike other scores. The sensitivity ≥95% for VNTs (condition of Baveno VI criteria for missed VNT ≤ 5%) was for VNT scores or tests: Baveno VI: 24.1% (of patients), PLR: 29.2%, ANTICIPATE: 31.5%, SCOUT 1: 34.8%, SCOUT 2: 37.8% (p < 0.001 between each test). This analysis also showed a significant interaction between BMI and etiology or prothrombin index. Thus, BMI of VNTs adjusted on covariates (by ANCOVA) was significantly decreased in NAFLD (p = 0.002) but significantly increased in alcohol (p = 0.009) vs no VNT (Figure).



Conclusion: The prevalence of VNTs varies according to etiology, liver function and fibrosis, and sex. The role of BMI is unmasked owing to a real interaction with etiology: negative influence in NAFLD and positive in alcoholic etiology. These new findings allow improving the performance and calibration of predictive scores for VNT and finally tests to rule out VNT.

SAT198
Direct acting oral anticoagulant use in cirrhosis patients: real-world bleeding and discontinuation rates

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Background and Aims: Previously published studies on the use of direct acting oral anticoagulants (DOACs) in patients with cirrhosis are limited by small sample size, short follow up, and inadequately validated cirrhosis diagnoses. In this study we systematically determine the characteristics, indications, and outcomes of verified cirrhosis patients of all severity classes taking DOACs.
Method: Patients from a large liver transplant center with documented cirrhosis were retrospectively evaluated for clinical characteristics, indications for DOAC use, and clinical outcomes. Standardized and validated definitions (ISTH) for all bleeding complications were used.
Results: 138 confirmed cirrhosis patients received DOACs. See table. The patients were exposed to 58,240 person-days (mean 422 days per patient) of DOAC treatment. 93 patients (68%) were CP B or C. 29 patients (21%) stopped therapy due to bleeding. The most common bleeding events were non-variceal upper and lower GI bleeding. No pretreatment laboratory parameters were predictive of bleeding on treatment including platelet count (p = 0.50), INR (p = 0.34), creatinine (p = 0.27), and MELD score (p = 0.22). Related bleeding rates were not different between CP class (p = 0.81), DOAC indication (p = 0.60), or DOAC dosage (p = 0.10). Patients with active malignancy (p = 0.01) were more likely to have major bleeding on therapy. Major bleeding was numerically more common in CP C patients due to a larger hemoglobin drop when bleeding was identified.

Characteristic	n (138)	(% of population)
Bleeding Complications		
Related Bleeding Events	45	33%
Major bleeding	11	8%
Clinically relevant non-major bleeding (CRNMB)	22	16%
Minor bleeding	12	9%
Stopped DOAC due to bleeding event	29	21%
Child Pugh Class (CP)		
A	45	33%
B	70	51%
C	23	17%
Indication for DOAC		
DVT/PE	47	34%
AF	44	32%
PVT	39	28%
Type of DOAC		
Apixaban	94	68%
Rivaroxaban	32	23%
Dabigatran	12	9%

Conclusion: Patients with cirrhosis have higher bleeding rates when taking long term DOACs than previously described. Pretreatment laboratory parameters, DOAC dose, and CP class were not predictive of bleeding although CP C and active malignancy are associated with major bleeding.

SAT199
Fluency is associated with hepatic encephalopathy using a common and easy language task

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Background and Aims: Current tools for neurocognitive evaluation in hepatic encephalopathy (HE) are limited, typically requiring a trained practitioner in an office setting and over 10 minutes to perform. We evaluated easy-to-obtain aspects of language as novel biomarkers for HE.
Method: We enrolled adult cirrhotic patients with fluency in English. Patients performed the psychometric HE score (PHES), a validated neurocognitive test in HE, and were audio recorded while describing

the Cookie Theft Scene from the Boston Diagnostic Aphasia Examination. The following variables were measured: words per minute (fluency), empty phrases (lacking obvious meaning), stutters, fillers ("um" or "uh"), pauses ≥2 seconds and tangential thoughts (irrelevant to image). Prior history of overt HE (OHE) was identified. A t-test compared language variables in those with and without minimal HE (MHE), defined as a PHES score≤−4.

Results: 40 cirrhotic patients (58% men) with mean MELD 16.5 (SD 7.8), aged 59.8 years (range 27–79) and with years of education 16.0 (SD 2.8) were audio recorded. Cirrhosis etiology was alcohol in 40%, NASH in 18% and viral in 23%. 23 (58%) patients had a history of OHE (OHE), while 17 (42%) did not. 13 (33%) patients met the PHES threshold for MHE at the time of study visit, while 27 (67%) did not. More patients with current MHE had a history of OHE than patients without MHE (92% vs. 41%, $p < 0.01$; Table 1). In the entire cohort, number of empty phrases ($r = -0.34$, $p < 0.05$) and number of words per minute ($r = 0.50$, $p = 0.001$) correlated with PHES score. Patients with MHE used fewer words per minute than those without (121 words/min vs. 141 words/min; $p = 0.02$). Number of empty phrases ($p = 0.27$), filler words ($p = 0.43$), stutters ($p = 0.45$), pauses ($p = 0.24$) and tangential thoughts ($p = 0.17$) did not correlate with the presence of MHE. Amongst the 23 patients with a history of OHE, number of words per minute correlated with PHES score ($r = 0.45$, $p < 0.05$). Amongst the 17 patients without a history of OHE, number of words per minute did not correlate with PHES score ($r = 0.03$, $p = 0.90$).

Table 1: Language Variables by Minimal Hepatic Encephalopathy Status.

	MHE§ (n=13)	No MHE (n=27)	P value
History of OHE*	92%	41%	<0.01
Words/minute	121	141	0.02
Empty phrases	0.42	0.18	0.27
Filler words	3.39	2.71	0.43
Stutters	0.39	0.71	0.45
Pauses	1.11	0.76	0.24
Tangential thoughts	0.17	0.04	0.17

Conclusion: Number of words per minute, or fluency, is associated with MHE. Modern technology permits straightforward and timely assessment of fluency. Future research should explore using fluency to predict future OHE and to evaluate treatment response.

SAT200

A smartphone app is feasible for outpatient ascites management

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Background and Aims: Ascites is a frequent, painful and dangerous complication of cirrhosis. Body weight is a reliable proxy for ascites volume. Therefore, daily weight monitoring is recommended to optimize ascites management. This pilot study evaluates the feasibility of a Smartphone app in facilitating outpatient ascites management.

Method: In this feasibility study, cirrhotic patients with ascites requiring active management were enrolled in the inpatient or outpatient setting. Patients were subsequently discharged with a Bluetooth-connected scale, which transmitted weight data to the PGHD Connect Smartphone App, and then via the cloud to the electronic medical record (EMR). Weights were monitored every weekday. In the event of a weight change ≥5lbs in 1 week, patients were called and administered a short symptom questionnaire, and providers received an email alert. The primary outcomes of this study were percentage of enrolled days during which weight data was successfully transmitted to the EMR, and the percentage of weight alerts which prompted a response by the provider.

Results: 78 cirrhotic patients were identified as potential candidates: 8 did not own a Smartphone, 23 were encephalopathic and were excluded. 1 declined to participate and 3 withdrew prior to discharge due to severe illness. 25 patients were enrolled: 12 (48%) were male and mean age was 57.6 years (range 35–81 years). 17 (68%) were enrolled as inpatients. Cirrhosis aetiology was non-alcoholic steatohepatitis in 44%, alcohol in 40% and viral in 12%. 15 patients opted to extend their participation beyond the initial 28-day study period. Weight data was successfully transmitted to the EMR during 71% of study enrolment days, with technology issues reported on 16% of days. Of a total 80 weight alerts to date, 39 (49%) were triggered by weight loss and 41 (51%) by weight gain. Providers acknowledged 71 (89%) weight alerts, and intervened in response to 38 (48%), for example by contacting the patient, scheduling clinic or paracentesis appointments, modifying the diuretic dose or requesting laboratory workup. 17 readmissions occurred during the study period.

Conclusion: We demonstrate feasibility of a Smartphone app in facilitating the management of ascites. We report excellent rates of patient and provider engagement. This innovation could enable early therapeutic intervention, decreasing the burden of morbidity and mortality among cirrhotic patients.

SAT201

Comparative study between spontaneous fungal peritonitis and spontaneous bacterial peritonitis in patients with end stage liver disease

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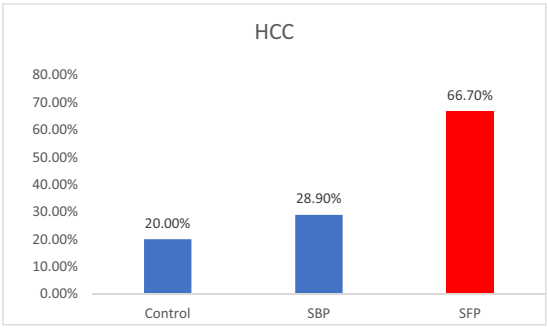
Background and Aims: Bacterial infections in end stage liver disease (ESLD) are common and associated with increased mortality. The aim of this study was to evaluate clinical and laboratory characters, risk factors, and outcome of fungal and bacterial peritonitis in cirrhotic patients with ESLD.

Method: This prospective cohort study enrolled 50 patients with liver cirrhosis and ascitic culture-positive spontaneous peritonitis, including 12 with SFP, and 38 culture-positive SBP, and 10 patients without clinical or laboratory evidence of peritonitis as a control group, during the study period, between 1st February 2018 and 30th May 2019. We compared the clinical, laboratory findings, Child–Pugh scores, MELD score, risk factors and mortality rates between patients with spontaneous peritonitis associated with fungal culture-positive ascites, and those with spontaneous peritonitis associated with bacterial culture-positive ascites.

Results: The mean duration of ESLD in the studied patients was 4.75 ± 1.8 year, 57 patients (95.0%) were Child score C and 3 patients (5%) were Child score B. The mean MELD score was 23.32 ± 5.49. All patients with evidence of peritonitis were Child C and mean MELD scores was 22 ± 5.7and 26.1 ± 4.5 in SBP and SFP groups respectively. Jaundice, GI bleeding and hepatic encephalopathy were highly significant clinical presentation and also highly significant predictors of mortality in SFP group compared to SBP and control group ($p < 0.001$). Lower level of Hg, S. albumin and platelets count and increased level of TLC, INR, and bilirubin was significantly higher in SFP group compared to SBP and control group.

Duration of ESLD and hospital admission was highly significant in SFP compared to SBP and control group. HCC was evident in SFP group 8/12 patients (66.7%) that was highly significant in comparison to SBP 11/38 (28.9%) and control group 2/10 (20%) ($p = 0.041$). Overall mortality rate among the studied groups was 27/60 (45%), the mortality rate was significantly increased in SFP group 9/12 (75%) compared to SBP16/38 (42.1%) and control group2/10 (20%) ($p = 0.03$). The mean MELD score was significantly increased in non-survival group 27.6 ± 4.0 compared to 19.2 ± 3.3 in survival group ($p = <0.001$). The duration of ESLD was significantly increased in non-survival group 5.7 ± 2.0 year compared to 4.1 ± 1.5 year in survival group p = (0.004)



Conclusion: Prolonged and severe underlying liver disease with a high Child- Pugh or MELD score, renal impairment, HCC, and onset of severe sepsis have reported as a risk factors in increased mortality in patients with SFP than in SBP. In SFP, mortality is associated not only with the severity of the underlying liver disease but also with delay in diagnosis and initiation of antifungal therapy. Further studies are needed to clarify the features of SFP and determine the effects of antifungal therapy on patient's outcome.

SAT202

Association between proton pump inhibitor use in hospitalized cirrhotics and development of hepatic encephalopathy and spontaneous bacterial peritonitis

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Background and Aims: Proton pump inhibitors (PPI) are commonly prescribed medications which are indicated in various different gastrointestinal (GI) diseases, including peptic ulcer disease, gastro-esophageal reflux disorder and upper GI bleeding. There is some evidence to suggest that PPI use in cirrhosis may predispose to the development of hepatic encephalopathy (HE) and spontaneous bacterial peritonitis (SBP), albeit with some controversy. We aim to conduct a retrospective epidemiological analysis of the association between PPI use in hospitalized patients with cirrhosis, and prevalence of HE and SBP.

Method: This was a retrospective cohort study of 600 adult patients (mean age 61.4 (SD = 12.2)) admitted the Ottawa Hospital between January 1, 2011 and December 31, 2015 with cirrhosis. A chart review was conducted and relevant information extracted.

Results: Average MELD-Na on admission was 16.2 (SD = 6.7). 14.8% of patients had a history of HE, 5.0% SBP, 7.8% with history of hepatocellular carcinoma and 1.0% with history of hepatorenal syndrome. 28.5% of patients had a history of varices, of which 11.0% had previous variceal bleeding. 69.3% of patients were on a PPI during their hospitalization. Not surprisingly, patients admitted with variceal bleeding were more likely to be exposed to PPI in hospital (97.2% vs 63.2%, $p < 0.01$) Patients with a diagnosis of cirrhosis prior to index admission were more likely to be on a PPI in hospital ($p = 0.001$) and on discharge ($p = 0.001$). Patients with ascites were less likely to be on a PPI than those without ascites (64.1% vs 77.6%, $p < 0.01$). There was no significant correlation between in hospital PPI use and MELD score ($p = 0.42$). Amongst patients on PPI in hospital, 85.9% remained on a PPI at discharge. Although numerically greater, no statistically significant differences were observed in terms of prevalence of HE (21.3% in patients on PPI vs 8.3% in those not on PPI ($p = 0.37$)), nor SBP (5.7% on PPI vs. 3.7% in those not on PPI ($p = 0.29$)).

Conclusion: We did not observe a significant difference in HE and SBP among this cohort of cirrhotic patients by in-hospital PPI use. We did however note significantly higher PPI use in patients with previous diagnosis of cirrhosis as compared to those who were newly diagnosed, as well as those whose admissions were related to bleeding. Patients with ascites had lower prevalence of PPI use. Prescribing patterns for PPIs in patients with cirrhosis warrant further attention, including clinical utility and longer-term risks and benefits of this therapy.

SAT203

Sarcopenia increases the risk of post transjuglar intrahepatic portosystemic shunt hepatic encephalopathy

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Background and Aims: Hepatic Encephalopathy (HE) is a potentially lethal complication and sarcopenia an undesirable consequence of chronic liver disease. Transjuglar intrahepatic portosystemic shunt (TIPS) procedure increases the risk of HE. We investigated the effects of sarcopenia on the incidence and outcome of HE after a TIPS procedure.

Method: Clinical, biochemical and follow-up data of patients who underwent TIPS procedure between 2010 and 2018 at the Institute of Liver and Biliary Sciences (ILBS), New Delhi, were extracted from the hospital information system (HIS). Single slice computed tomography (CT) images at L3 level of scans performed within 3 months prior to TIPS were analyzed using Slice-o-matic software to assess the skeletal muscle index (SMI)- expressed as skeletal muscle area (cm^2)/height (m^2). Sarcopenia was defined if SMI was <50 in males and <42 in females and overt HE as per West-Haven criteria.

Results: Of the 210 patients who underwent TIPS, complete information was available in 79 patients [Male: 68(86%); age: 50.5 ± 11.2 years; CTP: 9.29 ± 1.6; MELD: 15.7 ± 6.3; etiology - Alcohol: 44 (56%), NASH: 16(20%), others: 19(24%); TIPS indication - Ascites: 56 (71%); bleed: 23(29%)]. Overt HE developed in 29(37%) patients within a period of 1–9 months post-TIPS. Both the prevalence of sarcopenia (69% vs 44%; $p = 0.03$) and serum ammonia (177.6 ± 82.5 vs 115.5 ± 40.5 mmol/L; $p = 0.008$) were higher in patients who developed HE compared to those who did not develop HE. Patients with sarcopenia had 2.8 times higher risk of HE [OR (95% CI): 2.8 (1.08–7.4), $p = 0.02$]. The risk of multiple episodes of HE was 8.2 times higher in sarcopenics 31% (n = 13) than non-sarcopenics 5.4% (n = 2); [OR (95%CI): 8.2(1.68–40.5), $p = 0.009$].

Conclusion: Nearly one in 3 cirrhotic undergoing TIPS is sarcopenic. Sarcopenia reduces ammonia detoxification capacity and increases the risk of post-TIPS hepatic encephalopathy in patients with cirrhosis. Early and effective nutritional habilitation and physical training programs are vital for better outcome of TIPS in sarcopenic patients.

SAT204

Distinct features of the portalhypertensive syndrome in patients with advanced chronic liver disease due to non-alcoholic steatohepatitis

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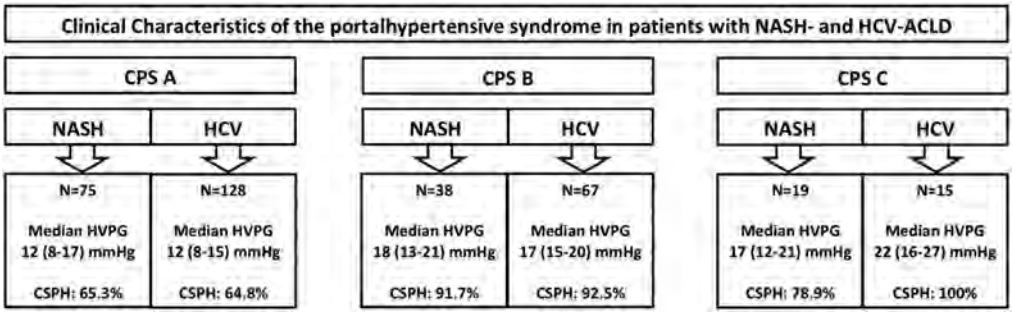

Figure: (abstract: SAT204)

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Background and Aims: Due to the global epidemic of obesity, non-alcoholic steatohepatitis (NASH) has become a leading cause of cirrhosis. Clinically significant portal hypertension (CSPH) is a major driver of decompensation and mortality; however, features of CSPH have not been systematically assessed in patients with advanced NASH.

Method: NASH patients with hepatic venous pressure gradient (HVPG) ≥6 mmHg were included. Clinical characteristics including data on gastroesophageal varices, splenomegaly, ascites and Child-Pugh score (CPS) were recorded. CSPH features were described in NASH patients stratified by CPS and compared to a cohort of HCV patients. Patients on non-selective beta-blocker therapy or with HCC were excluded.

Results: 162 patients with NASH (n = 43, 26.5%, subclinical portal hypertension [scPH: HVPG 6–9]; n = 119, 73.5% with CSPH [HVPG≥10 mmHg]) and 280 with HCV (scPH: 26.1%; CSPH: 73.9%) were included. CPS stage distribution were in NASH vs. HCV: CPS-A n = 75(53%) vs. n = 128 (61%), CPS-B: n = 38(44%) vs. n = 67(32%), CPS-C: n = 19(13%) vs. n = 15(7%).

Median HVPG in CPS-A was 12 (8–17) mmHg in NASH vs. 12 (8–15) mmHg in HCV (p = 0.723) in CPS-B: NASH:18 (13–21) mmHg vs. HCV: 17 (15–20) mmHg (p = 0.831); and in CPS-C NASH: 17 (12–21) mmHg vs. HCV: 22 (16–27) mmHg (p = 0.051). CSPH was detected in CPS-A NASH: 65.3% vs. HCV: 64.8% (p = 0.944); in CPS-B NASH: 91.7% vs. HCV: 92.5% (p = 0.864); and in CPS-C: NASH: 78.9% vs. HCV: 100% (p = 0.059), respectively. In compensated patients the prevalence of splenomegaly (NASH: 64.5% vs. HCV: 75.6%, p = 0.234) and gastro-esophageal varices (56.3% vs. 54.4%, p = 0.795) was similar in NASH and HCV, while thrombocytopenia was less common in NASH (58.8% vs. 77.9%, p = 0.002). In NASH-CSPH patients, the prevalence of severe/grade-III ascites was 11% vs. 5.3% in HCV-CSPH patients (p < 0.001). The median HVPG in patients with severe ascites was 19 (16–23) mmHg in NASH and 22 (15–28) mmHg in HCV (p = 0.285), respectively.

Conclusion: Two thirds of compensated NASH patients may suffer from CSPH. When stratified by hepatic dysfunction, HVPG values were similar in NASH and HCV cirrhosis. However, NASH-CSPH patients showed less thrombocytopenia while severe ascites was more prevalent despite similar HVPG values as compared to HCV patients.

SAT205

A novel, smartphone-based scleral image capture technique accurately determines serum bilirubin level and can be used for home-based monitoring of patients discharged from hospital, after an episode of acute decompensation

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Background and Aims: Acute decompensation (AD) of cirrhosis, including progression to acute-on-chronic liver failure (ACLF) is characterized by high 28-day mortality and hospital re-admission. Current non-invasive tools to predict new decompensation are limited, and costs of frequent outpatient visits are prohibitive. Given the importance of bilirubin levels in determining outcome, this study explores whether simple smart-phone based scleral image capture can accurately predict total serum bilirubin (TSB) levels, thereby serving as a home-based clinical monitoring tool.

Method: Consecutive patients admitted to Royal Free London with AD or ACLF over a year till August 2019 were screened based on predefined inclusion and exclusion criteria for an ongoing biomarker study, approved by institutional research ethics; 39 patients consented to participate. The scleral images were captured using the rear-facing camera of a dedicated Samsung® S8® phone. Images were then processed in MATLAB® (Mathworks®, r2018a), resulting in a numeric scleral colour value (SCV).

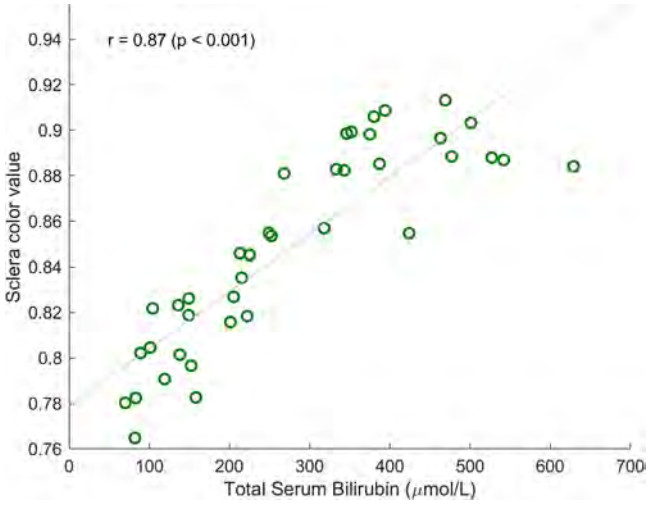

Figure 1: Correlation Between Sclera Colour Value and Total Serum Bilirubin.

Results: The mean patient age was 46.97 ± 8.6 years; 92% male. The mean creatinine and TSB were 96.3 ± 58.0 mmol/dl and 277.5 ± 150.9 mmol/dl, respectively. The most common cirrhosis aetiologies were alcohol (82%), NASH (12%) and viral hepatitis (2.5%), whilst a common cause of decompensation was alcoholic hepatitis in 41%. Around 92% patients had detectable ascites (U/S or clinical), and 48% patient had some grade of hepatic encephalopathy. The median MELD, MELD-Na and UKELD scores were 24.9 ± 4.7, 27.2 ± 4.7 and 47.1 ± 4.1, respectively. Figure 1, represents the scatter plot

between TSB and SCV. The mean SCV was 0.849 ± 0.04. The Pearson correlation coefficient was 0.87; 2-tailed significance of $p < 0.001$. This significant correlation between TSB and SCV was independent of aetiology of liver cirrhosis (alcohol vs. non-alcoholic $p < 0.001$), liver disease severity (Child B: $p = 0.002$; Child C: $p < 0.001$) and precipitant of decompensation (alcoholic hepatitis vs other precipitant ($p < 0.001$).

Conclusion: This novel smart phone based technique of scleral image capture can accurately predict serum bilirubin levels in patients with acute cirrhosis decompensation. Our results suggest this technology has the potential for home based TSB measurement for patients at risk of decompensation and need for early intervention.

SAT206

Degree of portal and systemic hemodynamic alterations predict repeated episodes of acute kidney injury and chronic kidney disease in patients with cirrhosis

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Background and Aims: Cirrhotics are predisposed to develop frequent episodes of acute kidney injury (AKI) which in about one-third of patients leads to chronic kidney disease (CKD). There is limited data on systemic and portal hemodynamic alterations and development of CKD in cirrhotics.

Method: Consecutive patients with cirrhosis and without AKI, with a complete record of baseline hemodynamics, were followed for identifying risk factors for the development of AKI episodes and CKD. Negative binomial regression and competing risk survival analysis were performed to identify risk factors for AKI episodes and CKD respectively.

Results: Cirrhotics [n = 2013, aged 50.1 ± 11.8 years, 80% males, mean hepatic venous pressure gradient (HVPG) 16.2 ± 5.8 mm Hg, systemic vascular resistance index (SVRI) 2292.5 ± 810.6 dynes.s/cm5/m2 and cardiac index (CI) of 3.71 ± 1.35 L/min/m2 were enrolled. Of these, 893 (44.3%) received beta-blockers (BB) (carvedilol- 78%, propranolol-22%; second HVPG in 495 patients) of which 219 (44.2%) were responders (R+). On follow-up, median 379 (IQR 68–869) days, AKI developed at an incidence rate of 0.37 episodes per person-year, 26% patients developed CKD and 8% died. A lower incidence of AKI [HR 0.18, 95% CI 0.10–0.34] and lower mean number of AKI episodes [0.05 ± 0.25 vs. 0.42 ± 0.868; $p < 0.001$] were observed in R+. The incidence of CKD [subdistribution hazard ratio (SHR) 0.74, 0.54–1.02] and mortality [HR 0.21,0.06–0.73] were also lower in HVPG R+. Lower CTP class, use of BB and higher SVRI were independent predictors of hemodynamic response. Higher HVPG [ratio of means (RM); 1.79, 1.32–2.41], lower SVRI [0.15, 0.11–0.20], higher CI [1.87, 1.36–2.57] alongside presence of diabetes [1.81, 1.34–3.39], higher MELDNa score[1.07, 1.04–1.10] and use of BB[0.63, 0.48–0.83] were independent predictors of cumulative AKI episodes on negative binomial regression analysis. The cumulative episodes of AKI (1.60. 1.07–1.26), diabetes (2.6,2.1–3.1), higher MELDNa (1.05,1.03–1.06), higher age (1.03, 1.02–1.04) and lower SVRI (0.74, 0.61–0.90) were independent predictors of CKD.

Conclusion: High portal pressure and hyperdynamic circulation predispose cirrhotics to repeated AKI episodes which is a risk factor for CKD. Response to beta-blockers reduced the risk of AKI and CKD and lowered mortality. The severity of vasodilatation was associated with lower hemodynamic response to BB and higher incidence of CKD. Routine monitoring and therapies targetting the vasodilatory state could improve the hemodynamic response to BB, prevent frequent AKI and reduce the risk of CKD development in cirrhotics.

SAT207

Long-term 20% albumin administration normalizes the plasma albumin binding capacity in patients with decompensated cirrhosis

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Background and Aims: Long-term albumin administration may be effective for treatment of cirrhotic patients. The PRECIOSA phase III trial (NCT03451292) is being conducted to assess the efficacy of one-year albumin treatment in the prevention of mortality in decompensated cirrhotic patients with ascites. The beneficial effects of albumin might be related to non-oncotic functions, particularly on its capacity to bind, transport and modulate biologically active molecules such as fatty acids, proinflammatory mediators and reactive oxygen species. In the present study we characterized the albumin binding capacity of patients with decompensated cirrhosis from the previous Pilot-PRECIOSA trial (NCT00968695) compared to healthy controls (HC), as well as the effects of i.v. albumin administration (Albutein® 20%, Grifols) on albumin binding capacity and its correlation with clinical parameters.

Method: Plasma samples from 22 patients included in the Pilot-PRECIOSA study were analyzed. This was a prospective, open-label and non-randomized clinical trial in decompensated cirrhotic patients with ascites, treated during 12 weeks with Albutein® 20% (low dose: 1 g/kg every 2 weeks; high dose: 1.5 g/kg weekly). Albumin binding capacity to Sudlow Binding Site II was determined using a specific fluorescent marker. AST and ALT were assessed by biochemical methods, and plasma renin activity (PRA) by radioimmunoassay. Results were expressed as median and IQR.

Results: Decompensated cirrhotic patients with ascites were not only hypoalbuminemic (1) but also its albumin presented a lower binding capacity respect to HC's one (n = 21) (77.5% [64.1–87.1] vs 96.3% [87.7–96.3]; $p < 0.0001$), which lead to a decrease in effective albumin for transport (18.7 mg/mL [12.9–28.7] vs 33.3 mg/mL [29.0–35.4] in HC; $p < 0.0001$). Albumin infusion increased the content of albumin with binding capacity up to HC-comparable levels ($p < 0.01$), being this increase dose-dependent. Moreover, the increased functionally-active albumin correlated with an improvement in AST and ALT levels and PRA over the course of treatment.

Conclusion: Albumin binding capacity was impaired in decompensated cirrhotic patients with ascites. Long-term albumin administration not only restored albumin concentration (1) but albumin transport capacity to normal levels, in parallel with improvement with circulatory dysfunction, estimated by PRA, and liver dysfunction. Our data suggest that an improvement of albumin transport may be a mechanism contributing to the beneficial effect of albumin treatment in cirrhosis.

Reference

1. *Gastroenterology* 2019;157:149–162.

SAT208

Aminoglycosides and metronidazole for the treatment of hepatic encephalopathy in adults with cirrhosis

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Background and Aims: The EASL/AASLD guidelines endorse the use of neomycin and metronidazole as second line treatment for overt

hepatic encephalopathy (HE), whereas the Italian guidelines state that these antibiotics should not used to treat HE, because of their potential for systemic toxicity. This study evaluates the utility of aminoglycosides and metronidazole for the management of HE in adults with cirrhosis.

Methods: Electronic/manual literature searches were undertaken for relevant RCTs. The results of the meta-analyses are presented as risk ratios (RR) with 95% confidence intervals (CIs). Bias control was assessed using CHBG domains and the certainty of the evidence using GRADE.

Results: Nineteen RCTs evaluated the aminoglycosides neomycin (n = 15), paromomycin (n = 3), and ribostamycin (n = 1). Treatment was given for 3 to 168 days. Comparators included: placebo (n = 3), NADs (n = 4), other antibiotics *viz.* rifaximin, erythromycin and ciproxin (n = 9), BCAAs (n = 2) and nicotinohydroxamic acid (n = 1). Only two trials had a low risk of bias; the certainty of the evidence was low or very low for all outcomes.

Nineteen trials reported mortality data, with no events in 11; 99 of 537 participants allocated to aminoglycosides died compared to 121 of 567 allocated to comparators (RR 1.06, 95% CI 0.67 to 1.69, I^2 63%, p = 0.79). Fifteen trials, with 1004 participants, reported data on HE; no differential beneficial or harmful effects were found in any of the trials (RR 0.95, 95% CI 0.71 to 1.28, I^2 38%, p = 0.75). Seventeen trials, reported on serious adverse events (SAEs), with no events in six; 139 of 507 participants allocated to aminoglycosides developed SAEs compared to 179 of the 532 allocated to comparators (RR 1.19, 95% CI 0.72 to 1.96, I^2 78%, p = 0.50) (Figure).

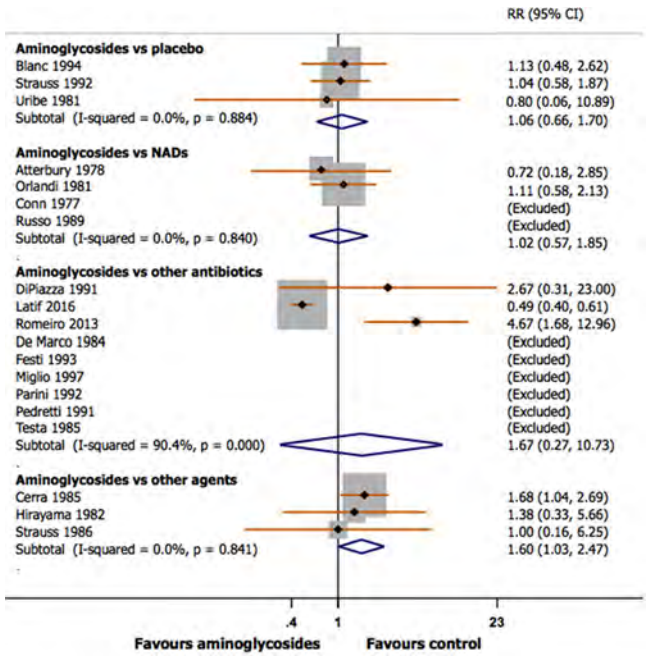

Figure: SAEs and aminoglycosides in patients with HE.

Three RCTs with 282 participants evaluated metronidazole with alternative therapies *viz.* vs. lactulose and LOLA (n = 1); vs. rifaximin and nitazoxanide (n = 1) and vs. rifaximin (n = 1). Metronidazole was associated with a higher risk of HE compared to LOLA in one trial (RR 2.25, 95% CI 1.17 to 4.33, p = 0.02) but otherwise the regimes were comparable.

Conclusion: No significant differences were observed in the utility of these antibiotics and a variety of comparators but the trials the quality of the evidence was low or very low. Recommendations can not be made on the basis of this review. Further well-conducted, RCTs are needed.

SAT209

Spleen stiffness and liver stiffness for predicting high risk varices in patients with compensated liver cirrhosis

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Background and Aims: To determinate the utility of spleen and liver stiffness (SS/LS) values measured by a 2D-SWE technique associated with spleen size (SSZ) as non-invasive markers for prediction of high risk varices (HRV) in patients with compensated liver cirrhosis.

Method: A prospective study was performed in 107 subjects with compensated liver cirrhosis, who underwent abdominal ultrasound, spleen and liver stiffness measurements (SSM, LSM) with a 2D-SWE technique from General Electric (LOGIQ E9) and upper endoscopy in the same admission. Reliable SSM and LSM were defined as the median value of 10 measurements acquired in a homogenous area and IQR/M <0.30. HRV were defined as grade II, III esophageal and gastric varices. Compensated liver cirrhosis was diagnosed based on clinical, biological and elastography criteria (liver transient elastography >12.5 kPa).

Results: We obtained reliable SSM by 2D-SWE in 103/107 subjects (96.2%) and reliable LSM in 104/107 subjects (97.1%). 101 subjects were included in the final analysis. 41/101 (40,6%) subjects had HRV. The mean SS, LS values and SSZ were significantly higher for patients with HRV as compared to those with first grade or no varices (16.78 ± 3.38 kPa vs. 12.69 ± 2.21 kPa, p < 0.0001; 14.13 ± 2.32 kPa vs. 11.4 ± 1.4 kPa, p < 0.0001; 14.54 ± 1.95 cm vs. 13.12 ± 1.66 cm, p = 0.0002). The best SS, LS and SSZ cut-off values for predicting the presence of HRV are presented in the following table:

Parameter	Cut-off	AUC	Se (%)	Sp (%)	PPV (%)	NPV (%)
Liver Stiffness	12.1 kPa	0.86	85.3	68.3	64.8	87.2
Spleen Stiffness	13.2 kPa	0.84	87.8	68.3	65.5	89.1
Spleen size	12.9 cm	0.71	85.3	48.3	53	82.9

In both univariate and multivariate analysis, SSM, LSM and SSZ were associated with the presence of HRV (all p < 0.001 for univariate analysis, respectively p = 0.0019, p = 0.0365 and p = 0.0046 in multivariate analysis). Using these factors as predictors, by multiple regression analysis we obtained the following score: 0.053* SS + 0.054* LS + 0.059* SSZ-1.84 with a cut-off value >0.31 (AUROC – 0.91; sensitivity-90%; specificity- 65%; PPV- 64%; NPV- 90%). By comparing the AUROC's our score performed better than spleen size for predicting HRV, but it's accuracy was similar to SS and LS by 2D-SWE (p = 0.0006, p = 0.1448; p = 0.2563).

Conclusion: SS, LS and SSZ are good non-invasive predictors of HRV, both separately or together.

SAT210

Natural history and outcomes of patients with liver cirrhosis complicated by hepatic hydrothorax

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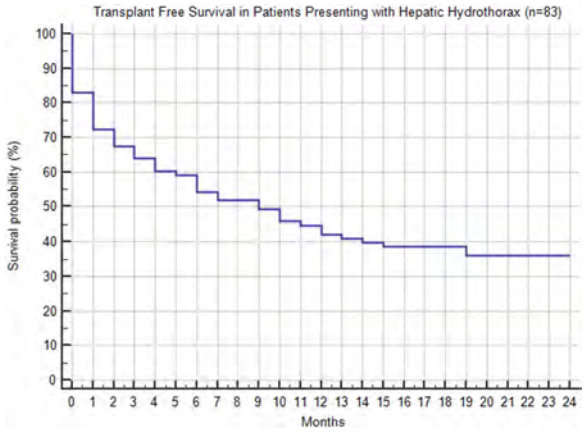
Background and Aims: Hepatic hydrothorax (HH) is an uncommon and difficult-to-manage complication of cirrhosis with no established clinical guidelines. We sought to define the clinical outcomes of patients presenting with HH managed with current standards-of-care.
Method: International Classification of Diseases-10 codes identified cirrhotic patients with HH presenting to 3 tertiary centres (Melbourne, Australia) from 2010 to 2018. HH was defined as pleural effusion in the absence of cardiopulmonary disease. Medical records were reviewed to determine baseline characteristics and survival. Primary outcome was 12-month mortality. The Kaplan-Meier method was used to calculate survival probability.
Results: 83 patients were included. Median age was 59 years (IQR 54–63), 57% were male and median MELD score was 29 (IQR 25–33). Common causes of cirrhosis were viral (33%), alcohol (27%) and non-alcoholic fatty liver disease (19%); 29% had hepatocellular carcinoma. Pleural effusions were typically right-sided (83%) and 73% had concurrent ascites. There were 169 hospital admissions for HH over the study period. Median length of stay was 11 days and 22% required intensive care unit admission. 89% and 7% patients were prescribed diuretics and non-selective beta-blockers respectively at presentation. Diuretic therapy alone was commenced in 13 (8%) presentations while 120 (71%) received diuresis and pleurocentesis (median 3L drained); 17% required blood products to facilitate pleurocentesis. 23 patients received intercostal drain insertion, 1 pleurodesis and 10 proceeded to transjugular intrahepatic portosystemic shunt insertion. 31 (37%) patients underwent liver transplantation (OLT). Significant complications were observed in 45% of admissions, including: infection [n = 25], hepatic encephalopathy [n = 19] and pneumothorax [n = 11]. 86% patients required re-admission within 6-months of index admission. The 12-month mortality rate was 29% (n = 24) and probability of transplant-free survival was 42% and 36% at 12- and 24-months respectively (Figure). All patients receiving OLT survived to 12-months.



Conclusion: Patients with decompensated cirrhosis and HH are a challenging population with a poor 12-month survival despite current treatments. Transplant assessment should be considered in all cases. There is a high prevalence of in-hospital and procedure-related complications and a minority of patients experience disease control with diuretic therapy alone.

SAT211

Acute or recent portal vein thrombosis in cirrhosis predicts a hidden or upcoming diagnosis of hepatocellular carcinoma

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Background and Aims: Portal vein thrombosis (PVT) is a common complication in cirrhosis. We assessed whether acute or recent PVT predicts hepatocellular carcinoma diagnosis.
Method: In an ICD9 retrospective study, total 560 PVT cases admitted to Hadassah Medical Organization 1982 until 2017 reviewed. Clinical and laboratory characteristics collected up the end of follow up (EoFU) to include acute or new onset PVT in cirrhotic patients, and to exclude hepatocellular carcinoma (HCC) or other active malignancy at the time of PVT diagnosis.
Results: Of 38 patients fulfilling the criteria, 12/38 diagnosed later with HCC at the post PVT follow up (31.6%). Early HCC diagnosed in 7/12 within 2 months (18.4% of the 38, mean age 60.3 ± 7.8 years, CHILD/MELD were 8.1 ± 2.9/15.4 ± 7.5, 25% alive at EoFU, group A) suggesting missed diagnosis of concomitant "PVT and HCC" at the PVT diagnosis. Late HCC diagnosed in 5/12 within 29.8 ± 36.7 months (13.2%, 59.9 ± 8 y, CHILD/MELD were 6.7 ± 0.6/12.8 ± 4.8, 40% alive at EoFU, group B). The rest 26 PVT patients did not had HCC by the end of follow up (68.5%, 56.8 ± 14.9 y, 58% alive at EoFU, CHILD/MELD were 7.7 ± 2.1/14.2 ± 5.6, group C). The most common underlying aetiology was viral (HBV/HCV) in HCC groups (early 66.7% and late 80%, respectively), while NAFLD led the non-HCC group (50%). 12% of non-HCC cases underwent transplantation, while all PVT/HCC cases were beyond transplant salvage.
Conclusion: Acute or recent PVT diagnosis in cirrhotic patients without evidence of HCC needs careful and immediate investigation for concomitant hidden HCC (by extending image modalities) followed by short-term HCC surveillance, mainly in viral aetiologies.

SAT212

The association of sarcopenia with myostatin, follistatin and irisin levels in cirrhotic patients: a multicenter cross-sectional study

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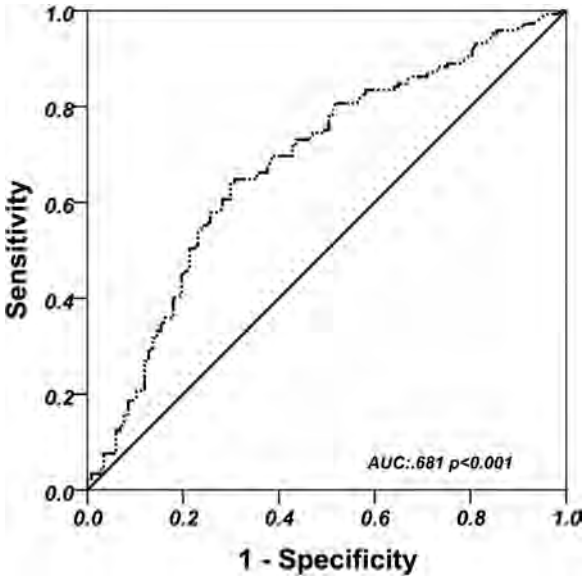
Background and Aims: Sarcopenia is independent predictor of mortality in cirrhosis. Because radiological analysis is the only current way to diagnose sarcopenia in cirrhosis, new practical diagnostic tests are needed to predict sarcopenia. We aimed to evaluate the efficacy of serum myostatin, follistatin and irisin levels as potential biomarkers for sarcopenia.
Method: A total of 262 patients followed up in 3 centers and 50 controls were included. Diagnosis of sarcopenia was confirmed when low muscle strength and low muscle mass were both detected. Muscle strength was measured by a handgrip test. Skeletal muscle mass assessed using skeletal muscle index (SMI) determined by calculating cross-sectional area of abdominal skeletal muscle at L3

level. Liver-specific subjective global assessment (SGA) was used to consider the nutritional status.
Results: Our study cohort had a median age of 58 years and included 139 (53.1%) males, whereas controls had a median age of 55 years and included 25 (50%) males. The median MELD and Child scores were 6.3 [3.5–9.95] and 6 [5–7] respectively. Muscle weakness was observed in 168 (64.1%) and decreased SMI was found in 214 (81.7%) patients. Eventually, a total of 145 (55.3%) patients were diagnosed as sarcopenia and this result was irrespective of nutritional status (SGA A, B, C) or gender. Serum myostatin levels were significantly higher in patients compared to controls 22.4 [9.2–35.8] vs. 2.2 [1.0–3.1 ng/dl $p < 0.001$) whereas serum irisin and follistatin levels showed no significant difference. While follistatin levels showed no significant difference between sarcopenia and non-sarcopenia groups, serum myostatin levels were significantly higher and serum irisin levels were significantly lower in the sarcopenia group (29.4 [14.8–41.2] vs. 14.3 [6.2–27.1] ng/dl $p < 0.001$ and 36.8 [15.8–103.7] vs. 54.8 [24.4–149.1] ng/dl $p < 0.01$). In order to detect the differentiating power of miyostatin levels for sarcopenia, we performed ROC analysis and AUC was 0.681. (Optimal cutoff value 23.3 ng/mL; sens 64%, spec of 70%). Serum myostatin showed positive moderate correlations with MELD and Child scores. ($r = 0.446, P < 0.001$; $r = 0.545, P < 0.001$). In BMI adjusted ANCOVA analysis, myostatin was independently higher in the sarcopenia group ($p < 0.001$)



Conclusion: Circulating miyostatin and irisin, but not follistatin are promising practical biomarkers that can be used in the diagnosis of sarcopenia in cirrhosis.

SAT213

A prospective evaluation of the Bristol prognostic score: poor sensitivity and specificity in a non-Bristol cohort

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Background and Aims: People with end-stage liver disease often have an unpredictable trajectory throughout the course of their illness which can make anticipatory care planning difficult. The Bristol Prognostic Score (BPS, Hudson et al, *Frontline Gastroenterol.* 2017) was developed to identify patients with decompensated liver disease likely to die within one year, to allow consideration of palliative care input. We sought to prospectively evaluate the performance of the score amongst an inpatient cohort in a non-transplant Scottish gastroenterology unit.
Method: Inpatients with decompensated liver disease in our unit as of the 1st of March 2017, and those admitted up to July 2017, were prospectively recruited. Admission BPS was calculated (based on Child's C, >2 admission in last 6 months, ongoing alcohol in ArLD, exclusion from transplant, WHO performance status 3 or 4). Electronic case notes were reviewed and mortality noted. Sensitivity, specificity and positive predictive values for BPS ≥3 were calculated. Frequency of BPS scores and 1 year mortality were compared against the original Bristol cohort using chi-square.
Results: 50 patients were studied. One emigrated and was excluded thereafter. 41 of the remaining patients (83.7%) had alcohol-related liver disease and 29 were male (59%). The median age was 55 (range 31–81, IQR 16).
33 (67.3%) were BPS positive (≥3/5). 19 (38.8%) of patients were dead at one year post admission, 12 in the BPS positive group. The sensitivity, specificity and positive predictive value of a positive BPS score for one year mortality were 63.2%, 30% and 36.4% respectively. Comparisons of our cohort compared with the Bristol cohort are shown in the table below.

Table: Number of patients stratified by BPS status and 1 year mortality

	Current cohort *n* (%)	Bristol cohort *n* (%)	
BPS ≥ 3	33 (67.3)	32 (43.8)	$p < 0.02$
1 year Mortality	19 (38.8)	36 (49.3)	$p = 0.33$
Sensitivity	63%	72.2%	
Specificity	30.8%	83.8%	
Positive Predictive Value	45.5%	81.3%	

Conclusion: Our patients had a higher prevalence of a positive BPS but not significantly different 1 year mortality compared with the original Bristol cohort. 7/19 (36.8%) of deaths occurred in the BPS negative group. Overall these results demonstrated poor sensitivity, specificity and a low positive predictive value for one year mortality in patients with a BPS ≥3. Prospective validation of the BPS in individual settings should be undertaken before being considered as a tool in routine care.

SAT214

Blood and ascites pharmacokinetics of meropenem in patients with nosocomial spontaneous bacterial peritonitis and decompensated liver cirrhosis

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Background and Aims: Nosocomial spontaneous bacterial peritonitis (nSBP) is a severe complication in patients with decompensated liver cirrhosis. Inadequate concentrations of antibiotics may cause treatment failure and drug resistance, which has been increasing over the last years. However, there are quite limited data available on pharmacokinetics of carbapenems in patients with advanced liver disease, in particular with regard to the ascites fluid. The aim of the study was to investigate the Meropenem kinetics in blood and ascites in patients with nSBP.
Method: Seven patients with nSBP, decompensated liver cirrhosis and indication for Meropenem treatment were prospectively recruited. Plasma and ascites samples were collected at baseline as

well as 15, 30, 45, 60, 120, 240, 480, 510 and 960 minutes after the first Meropenem infusion at day 0 and at the same time points on an additional day >48 hours after start of treatment. In addition, plasma and ascites samples were obtained once on each day previous to Meropenem infusion. Overall, 100 plasma and 110 ascites samples were available for the assessment of Meropenem drug level. Minimum inhibitory concentration (MIC) was defined as 2 mg/l referring to Enterobacteriaceae (EUCAST).

Results: Three women and four men with a median age of 51 years and median MELD score of 22 were included. Median creatinine was 197 µmol/l, weight 67 kg and height 1.72 m. Median ascites drainage volume was 1600 ml/day. The median Meropenem dosage was 3 g/day. Some remarkable pharmacokinetic differences were documented when comparing Meropenem levels in plasma and ascites. The maximal concentration (Cmax) was higher in plasma than in ascites (44.7 mg/l vs. 26.0 mg/l, p = 0.001). While median time to Cmax was only 30 minutes in plasma, it took 120 minutes in ascites (Figure). However, therapeutic concentration (>4xMIC) was achieved already after 15–45 minutes in ascites and remained above this threshold for at least 44% of the time in all patients. Of note, at all times measured concentrations in blood plasma and ascites were higher than the MIC in all analysed patients and did not yield toxic levels.

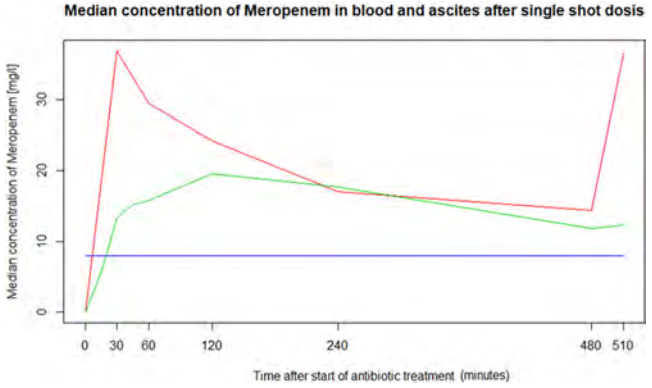

Figure: Meropenem concentration in blood (red) and ascites (green) shown. The 4xMIC is displayed in blue.

Conclusion: Although distinct differences between Meropenem pharmacokinetics in ascites and blood exist, the concentration never falls under the MIC in both compartments. Current nSBP treatment strategy with Meropenem seems to be safe and achieves sufficient drug levels in ascites.

SAT215

Diagnostic performance of contrast-enhanced CT for the diagnosis of portosinusoidal vascular disease: a case-control study

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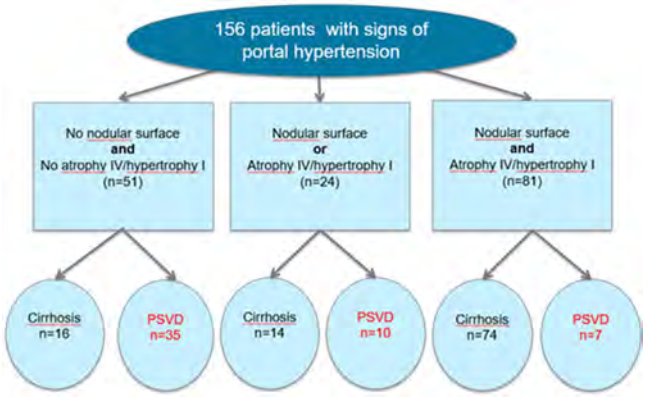
Background and Aims: Porto-sinusoidal vascular disease (PSVD) is a rare cause of portal hypertension. Imaging findings have been described as associated with PSVD, but their diagnostic value has not been established and their relationship with histological lesions is unknown. The aim of this study was to assess diagnostic performance of contrast-enhanced CT (CECT) features in patients with PSVD and signs of portal hypertension, as compared to patients with cirrhosis.

Method: This retrospective monocentric case-control study included all patients with PSVD, according to VALDIG criteria, who underwent a liver biopsy between 2011 and 2018 and performed CECT in the year before or after liver biopsy. Each patient with PSVD was matched for the severity of ascites with 2 patients with histologically proven cirrhosis without hepatocellular carcinoma outside Milan criteria. PSVD biopsies were reviewed by an expert pathologist and elementary lesions classified according to pre-specified criteria. CT images were reviewed by 2 independent radiologists, not aware of the liver disease, and classified according to pre-specified criteria.

Results: 52 patients with PSVD [23 women; 60 years (43–68); MELD 9 (7–10)] and 104 patients with cirrhosis [23 women; 62 years (52–68); MELD 11 (8–16)] were included. In patients with PSVD, as compared with patients with cirrhosis, abnormalities of intrahepatic portal branches and/or extrahepatic portal vein (p = 0.047), mesenteric and/or splenic vein thrombosis (p = 0.01), inter-hepatic vein collaterals (p = 0.005), and hepatic veins near to the capsulae (p = 0.002) were statistically more common, and spleen was larger (p = 0.011). In patients with PSVD, simultaneous atrophy of segment IV with hypertrophy of segment I (p < 0.0001), and a nodular liver surface (p < 0.0001) were less common. Using binary logistic regression, imaging features associated with PSVD were an absence of simultaneous atrophy of segment IV with hypertrophy of segment I, and an absence of nodular liver surface (OR = 4.7 (IC 95% 1.8–12.3) p = 0.002 for both) (Fig.). Combining the latter 2 criteria had a sensitivity of 67% and a specificity of 87%. Among patients with PSVD, no significant associations between pathological and imaging data were found.



Conclusion: In patients with signs of portal hypertension, absence of simultaneous atrophy of segment IV with hypertrophy of segment and absence of nodular surface of the liver should raise suspicion of PSVD.

SAT216

Broad defect in energy metabolism drives immune dysfunction in cirrhosis and cirrhosis associated sepsis

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Background and Aims: Immune dysfunction have been shown to be associated with increased incidences of sepsis with high mortality in cirrhosis. Underlying cause of immune paralysis in response to infection in cirrhosis is not defined. Energy metabolism has recently

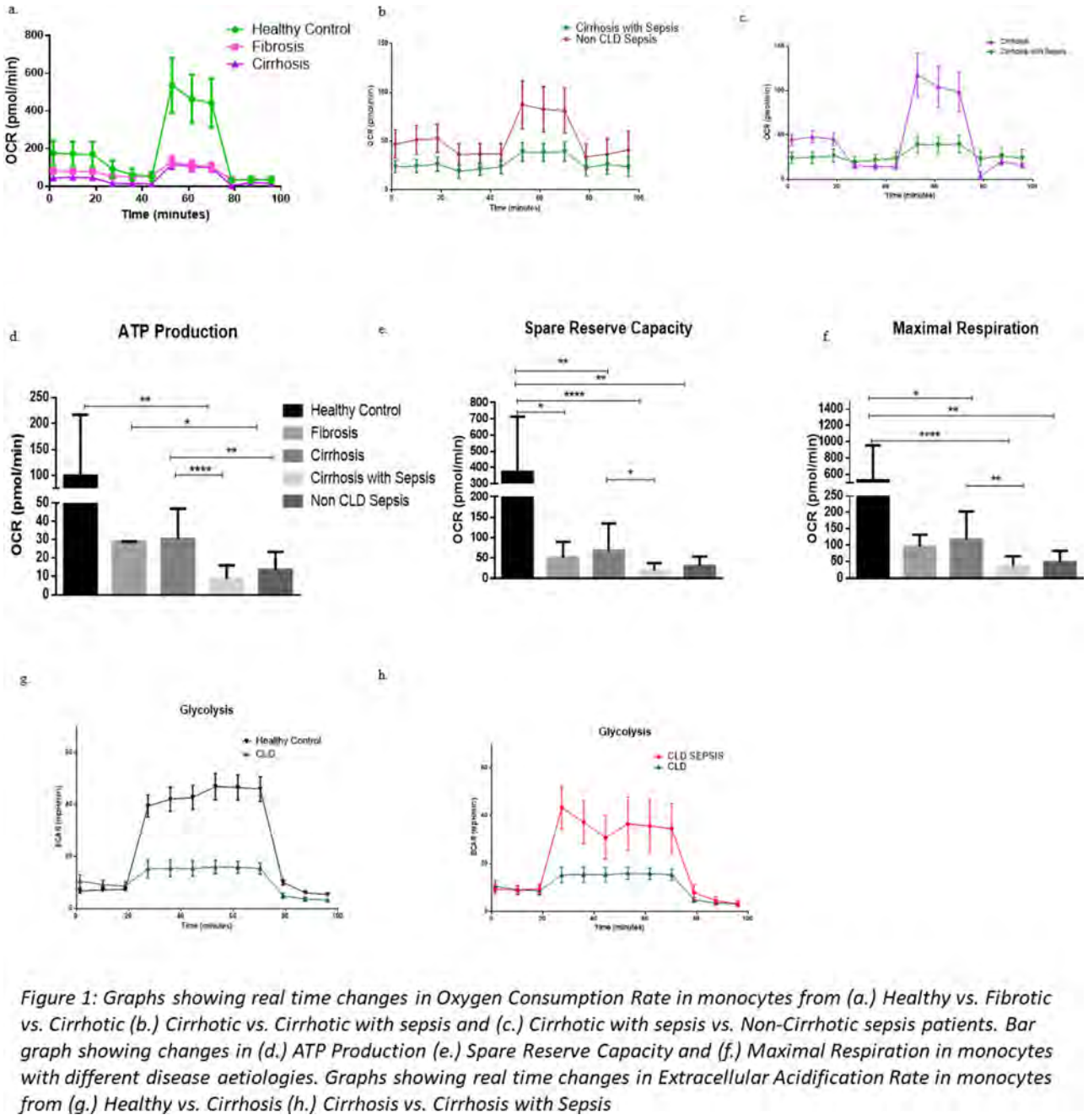

Figure 1: Graphs showing real time changes in Oxygen Consumption Rate in monocytes from (a.) Healthy vs. Fibrotic vs. Cirrhotic (b.) Cirrhotic vs. Cirrhotic with sepsis and (c.) Cirrhotic with sepsis vs. Non-Cirrhotic sepsis patients. Bar graph showing changes in (d.) ATP Production (e.) Spare Reserve Capacity and (f.) Maximal Respiration in monocytes with different disease aetiologies. Graphs showing real time changes in Extracellular Acidification Rate in monocytes from (g.) Healthy vs. Cirrhosis (h.) Cirrhosis vs. Cirrhosis with Sepsis

Figure: (abstract: SAT216)

shown to guide the inflammatory and resolving function of monocytes in response to infection. our aimed to see the effect of cirrhosis on energy metabolism of monocytes and on its function

Method: Mitochondrial respiration and glycolysis of monocytes were analysed in fibrosis (F2 F3) patients (n = 6), cirrhosis without sepsis (CLD,n = 18), cirrhosis with sepsis (S-CLD,n = 23), non-cirrhotic sepsis patients (NCS,n = 10) and healthy(HC,n = 17). Phagocytic function of monocytes was assed using Phagocytosis Kit.

Results: Monocytes from fibrotic and CLD patients showed significant loss in mitochondrial potential compared to HC (fig 1a). Sepsis with cirrhosis resulted in further decrease in mitochondrial bioenergetics (Fig 1b-c). Sepsis was associated with significant decrease in cellular ATP production ($p < 0.005$) (fig 1d). S-CLD showed decrease in spare reserve capacity and maximal respiration compared to CLD ($p < 0.05$, fig 1e-f). Inhibition of mitochondrial ATP production in healthy monocytes significantly decrease ($p < 0.005$) their phagocytosis. In comparison to healthy, cirrhotic monocytes showed decrease ($p < 0.0001$) in phagocytic activity which further dampen ($p < 0.001$) with sepsis. Together suggesting loss of mitochondrial respiration leads to defect in monocytes phagocytosis in cirrhosis. Monocytes from CLD patients showed reduced glycolysis compared to HC (fig 1g) and showed decrease production of inflammatory cytokines (TNF-alpha, IL-1beta) in response to LPS. In cirrhotic sepsis, while there is rapid increase in glycolysis on injecting glucose, this rapidly decreases with time, suggesting glucose intolerance (fig 1h). In comparison to NCS cirrhotic monocytes show t impairment in both glycolysis and mitochondrial respiration

Conclusion: Our data suggests that chronic liver injury compromises bioenergetic potential of monocytes. Infection further dampen the energy metabolism of monocytes in cirrhosis leading to their

functional exhaustion. This might be responsible for poor resolution of infection and increased mortality in septic cirrhosis. Restoring bioenergetic potential of monocytes in CLD and CLD-Sepsis may result in improved outcomes in these patients.

SAT217

A nurse-led albumin infusion service reduces the need for therapeutic paracentesis in the outpatient day procedure setting

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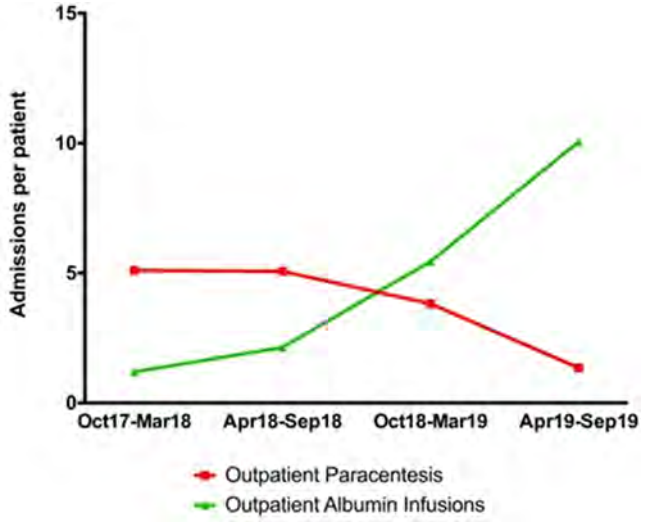
Background and Aims: Recent evidence has suggested a significant benefit from regular albumin infusions in patients with cirrhosis. We initiated a nurse-led service for patients that gradually began arranging regular albumin infusions for patients with cirrhosis and ascites from late 2017. We aimed to observe the take-up and impact of this service on day procedure admissions for therapeutic paracentesis over the last 2 years.

Method: A nurse-led albumin infusion program was gradually introduced as patients began being referred by their treating Hepatologist at a tertiary liver centre. Inclusion criteria were patients with cirrhosis and ascites admitted under Gastroenterology to the day procedure ward for either therapeutic paracentesis of at least 1L, or intravenous albumin infusions between 01/10/2017–30/09/19. As per standard practice, 100 ml of 20% concentrated albumin was given for either every 2L of ascites drained, or 2 × 100 ml per albumin admission. Statistical analysis included linear regression, with a $p < 0.05$ considered significant. Hospital coding was reviewed to ensure there was no corresponding increase in inpatient admissions.

Results: 460 unique patient episodes were documented in 28 patients over 2 years. A median 12.5 patients (range 10–17) had admissions to the day procedure centre for either paracentesis or albumin throughout each 6 month period. The average paracentesis/pt decreased during each 6 month period from 5.10 in the first 6 months to only 1.35 in the most recent period ($r^2 = 0.84$, $p = 0.08$), whilst admissions for albumin infusions per patient significantly increased from 1.2 to 10.1 ($r^2 = 0.93$, $p = 0.04$) (figure 1). Neither the average volume of ascites drained with each paracentesis ($r^2 = 0.51$, $p = 0.29$) or overall albumin volume per patient ($r^2 = 0.81$, $p = 0.10$) have significantly changed. Inpatient admissions with ascites did not increase, with a gradual drop from 30 to 25 per 6 month period over the 2 years ($p = 0.29$).



Conclusion: We report the successful introduction of a nurse-led outpatient albumin infusion service. With increasing use of albumin, there has been a corresponding reduction in need for therapeutic paracentesis without any subsequent increase in inpatient activity.

SAT218

Increased levels of soluble mannose receptor are associated with poor outcome in cirrhosis: results from a 2-year longitudinal study

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Background and Aims: Activated hepatic macrophages play a key role in inflammation and fibrosis progression in chronic inflammatory liver diseases. In cross-sectional studies the macrophage activation marker soluble mannose receptor (sMR) is a promising prognostic marker for occurrence of cirrhosis-associated complications. However, the development in sMR levels over time has never been assessed in patients with cirrhosis. We therefore aimed to investigate changes in sMR over a 2-year period and the association with poor outcome.

Method: 61 cirrhotic outpatients (Child class: A = 9, B = 44, C = 8) were included in this 2-year longitudinal study. Clinical evaluations and biomarkers including sMR were assessed at 0/6/12/18/24 months. Patients were followed-up with registration of liver transplantation (LT), and death.

Results: We found a stepwise increase in baseline sMR with increasing Child classes CP-A: 0.21 mg/L (0.13–0.35), CP-B 0.36 mg/L (0.28–0.44), CP-C 0.83 mg/L (0.53–0.94), $p < 0.001$. During a median follow-up of 30 months 4 patients underwent LT and 19 patients died. Within the initial six months 4 patients underwent LT and 4 patients died. These patients had significantly higher baseline median sMR 0.83 mg/L (IQR:0.52–0.93) and 0.87 mg/L (IQR:0.47–1.33)) than those without events 0.31 mg/L (IQR: 0.23–0.42), $p = 0.003$ and $p = 0.006$, respectively. Additionally, we found significantly increasing sMR levels over time in the 15 patients who died and had repeated measurements from baseline median sMR 0.40 mg/L (IQR:0.29–0.48) to last visit median sMR 0.46 mg/L (IQR: 0.33–0.53) whereas patients without events had a slightly decrease in sMR levels over the 2-years with a last visit median sMR 0.26 mg/L (IQR:0.20–0.35), $p = 0.02$ for the difference in delta sMR and $p = 0.002$ for the difference in last visit sMR.

Conclusion: The sMR levels increase over time in cirrhotic patients who die during follow-up. Moreover, increased sMR levels are associated with poor both short-term and long-term outcome. This further emphasize and support that macrophage activation and inflammation are key components in disease progression and poor outcome in cirrhosis. Moreover, sMR seems a promising prognostic marker and potentially also for treatment response in patients with liver cirrhosis.

SAT219

MRI-derived myocardial extracellular volume is closely associated with markers of collagen formation in cirrhosis

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Background and Aims: Fibrotic remodeling of the extracellular matrix is a key component in the development and progression of liver cirrhosis. Contrast-enhanced MRI with quantification of the

extracellular volume (ECV) has proven to be closely related to presence of histological fibrosis in both the liver and the heart. Recently, we reported a strong interrelation between myocardial and hepatic ECV in patients with cirrhosis. We therefore hypothesized that a parallel accumulation of cardiac fibrosis is a likely contributing mechanism of cirrhotic cardiomyopathy. Our aim was to investigate the role of collagen turnover on myocardial ECV in patients with cirrhosis.

Method: We prospectively included 47 cirrhotic patients. All patients underwent contrast-enhanced MRI with T1-mapping and quantification of myocardial and hepatic ECV, and assessments of inflammatory biomarkers such as sCD163, sMR, IL-6 and IL-8, and serological biomarkers of collagen formation and degradation comprising PRO-C3, PRO-C5, PRO-C6, C4M, C5M, and LG1M.

Results: Myocardial ECV increased in relation to disease severity in cirrhosis. Myocardial ECV was closely correlated with markers of collagen formation: PRO-C3 ($r = 0.43$, $p = 0.002$), PRO-C6 ($r = 0.40$, $p = 0.004$) and markers of inflammation: sMR ($r = 0.43$, $p = 0.003$), IL6 ($r = 0.46$, $p = 0.001$). Moreover, myocardial ECV correlated with hepatic ECV ($r = 0.48$, $p = 0.001$). In a multivariate analysis, myocardial ECV was predicted by PRO-C6, IL-6 and sMR.

Conclusion: Myocardial ECV is increased in patients with advanced cirrhosis and the strong correlations with markers of collagen formation and hepatic ECV suggest that fibrogenesis is concomitantly activated in the cirrhotic liver and heart. Myocardial ECV can easily be determined by contrast-enhanced MRI and may reveal the degree of cardiac fibrosis. This method therefore represents an important tool for further insight into the role of fibrogenesis in the development of structural abnormalities in the heart leading to cirrhotic cardiomyopathy.

SAT220

FIB-4 and APRI-scores predict survival in patients with transjugular intrahepatic portosystemic stent shunts

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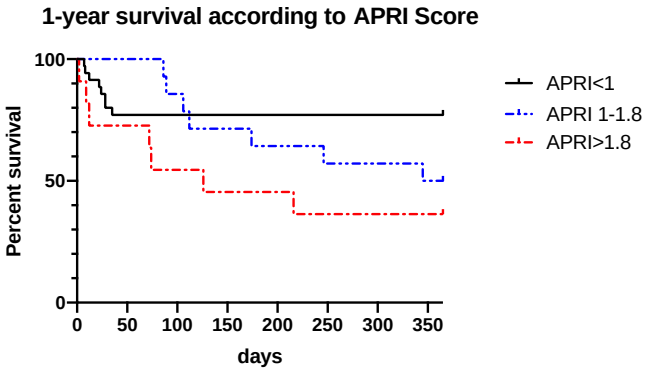
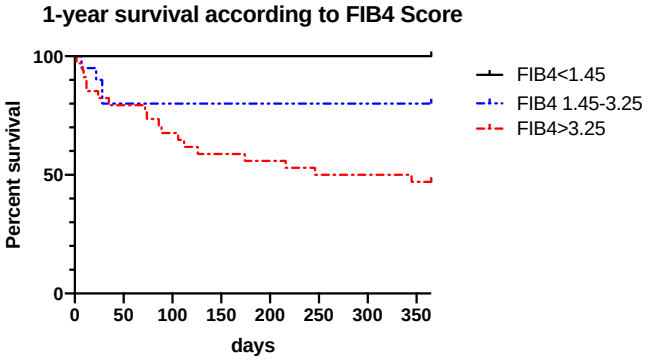
Background and Aims: Transjugular intrahepatic portosystemic shunt (TIPS) is a standard therapy in patients with liver cirrhosis. Interventional techniques and type of shunts have changed during the last 15 years. It is crucial to define easy and reliable factors associated with TIPS outcome, which however, may have different values depending on the shunt type and patient cohort. We here studied a homogenous single center cohort of TIPS patients and investigated predictors of patient survival.

Method: We analyzed a total of 100 consecutive patients with liver cirrhosis evaluated for TIPS, which has been placed in 87 patients by two radiologists between January 2017 and November 2019. TIPS diameter was <8 mm in 19 patients, 8 mm in 26 patients, and >8 mm in 42 patients. Major indication for TIPS was a hydropic decompensation (82/100 patients). Patients were followed for a median of 216 days (range 2–1012).

Results: The majority of patients was male (57/87). Median age was 57 years (range 20–88), median BMI was 25,4 kg/m^2. Child Pugh A/B/C class were 25/55/7 patients. Patient survival after 3, 6 and 12 months was 82%, 75% and 70% respectively. Acute hepatic decompensation, defined as bilirubin increase >5 g/dl as well as INR decrease, occurred within 3 months after TIPS in 9 cases. In univariate analysis, neither bilirubin nor INR or liver enzymes alone were associated with 6 and 12 months post-TIPS survival. However, both FIB-4 and APRI scores were associated with overall survival. The hazard ratio for death at 1 year was 3.5 (95% Confidence intervals 1–11) for patients with a FIB-4 score of >3.25 compared to <1.45, and 4.7 (95% Confidence intervals 1–16) for an APRI score of >1.8 compared to patients with an APRI of <1.





Conclusion: A combination of markers reflecting portal hypertension and biochemical disease activity predicts long-term outcome after TIPS with most recent shunts using covered stents.

SAT221

Real-world effectiveness of piperacillin/tazobactam-based therapies for spontaneous bacterial peritonitis

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Background and Aims: Current guidelines recommend empiric therapy with piperacillin/tazobactam (PTZ) for spontaneous bacterial peritonitis (SBP) at low risk for multi-drug resistant organisms (MDROs) based on in vitro antimicrobial resistance data. However, controlled trials of PTZ-based regimens for SBP are lacking and real-word data are sparse.

Method: In 2015 we implemented standard operating procedures for empiric antibiotic therapy of SBP at our department, advocating treatment with PTZ ± linezolid (LZD) for empiric therapy of SBP at low risk for Gram-negative MDROs, after using predominantly third generation cephalosporins (TGC) before. In order to assess the efficacy of PTZ-based regimens, we evaluated microbial resistance, cytologic response, treatment failure, and mortality in patients receiving TGC or PTZ-based therapies for SBP.

Results: 81 empirical treatments with PTZ-based regimen (44 PTZ, 37 PTZ + LZD) and 81 historical treatments with TGC were included. SBP was community-acquired in 48% of episodes (53% in TGC vs. 43% in PTZ-based regimens; $P = 0.27$). 71 (44%) episodes were culture-positive with a low prevalence of TGC-resistant Gram-negatives (6 ESBL-producing enterobacteriaceae) and a high prevalence of TGC-resistant Gram-positives (11 enterococci, 1 MRSA, 4 listeriae, 2 others).

Therapy failure resulting in antimicrobial therapy escalation was observed in 6 (16%) episodes treated with PTZ + LZD, 22 (50%) episodes treated with PTZ monotherapy, and 30 (37%) episodes treated with TGC monotherapy, respectively (p = 0.006). This was due to a low antimicrobial resistance rate in patients treated with PTZ + LZD (0/17 [0%]) vs. PTZ alone (5/21 [24%]) or TGC (10/33 [30%]) (p = 0.04) alongside low rates of cytological non-response (5/32 [16%] in PTZ+LZD vs. 8/33 [24%] in PTZ alone vs. 10/36 [28%] in TGC alone; p = 0.48). Therapy escalation because of clinical decision in the absence of resistance or cytological non-response was rare in patients treated with PTZ+LZD (1/37 [3%]) vs. PTZ monotherapy (11/44 [25%]) or 3GC (12/81 [15%]) treatment (p = 0.02).
The need for antimicrobial therapy escalation was associated with poor 30-days survival (60% vs. 83%; p = 0.001 log-rank). However, short-term survival did not significantly differ according to empirical treatment (79% PTZ+LZD vs. 70% PTZ vs. 75% TGC; p = 0.78).
Conclusion: These real-world data support the use of PTZ-based empirical therapies for SBP in settings of low rates of Gram-negative MDROs. PTZ+LZD combination therapy is associated with low rates of therapy failure.

SAT222

Etiology and diagnosis of ascites: contemporary cohort study in a secondary care setting

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Background and Aims: Studies performed in specialist centers more than 25 years ago reported liver cirrhosis (80–85%) as main etiology of ascites and diagnostic accuracy of serum-ascites albumin gradient (SAAG) greater then 11 to identify portal hypertension as cause up to 97%. This has impact on clinical decision-making and guidelines have prioritized particular tests based on their utility in routine practice. We aimed to describe the contribution of different etiologies of ascites in a contemporary cohort of patients and to test validity of SAAG and cytology in this cohort.
Method: Using the data from a National Health Service hospital providing secondary care to a population of 700,000, patients with a primary or secondary diagnosis of ascites were identified. Adult patients above age of 18 year, from May 2013 to April 2018 with confirmed ascites on ultrasound or CT scan were included. Patient with peritoneal fluid collection as an immediate or late manifestation of acute abdomen or postoperative complication were excluded (surgical cases).
Results: Over a period of 5 years, 286 patients [F:148] presented with new onset ascites. We excluded 122 surgical cases, and included 164 medical cases. Out of 164 cases, 90 (55%) had liver cirrhosis [Alcohol related liver disease 58, non-alcoholic fatty liver disease 21, chronic viral hepatitis 4, Auto immune liver diseases 3, and cryptogenic cirrhosis 4], 29% had malignancies [gynecological: 12, Gastrointestinal: 25 and others: 11], 6% cardiac failure (CF), 3% End stage renal disease (ESRD) and 7% others etiologies. We further divided participants into high SAAG (≥11) and low SAAG (<11) groups. SAAG was done in 116 patients. In high SAAG group out of 83 (71%) patients, 65 (78%) had liver cirrhosis and 6 (7%) have cardiac failure. On applying foster 2 by 2 contingency test, high SAAG (≥11) was 78% sensitive, 52% specific and had diagnostic accuracy of 64% in identifying portal hypertension as cause of ascites in this group. In low SAAG group (<11) out of 33 (29%) patients, 13 (40%) have malignant ascites and 5 (15%) had ESRD. In study cohort 29 (18%) patients had hepatic portal pressure gradient (HPVG) measured, of these 24 patients had a HPVG of >10, in this group high SAAG (≥11) was 90%, sensitive for portal hypertension. In patients with malignant ascites 40 patients (83%) had ascitic cytology checked out of this 20 (50%) has positive cytology for malignancy.
Conclusion: In a contemporaneous medical cohort of patients with ascites, underlying etiology and validity of currently available tests (SAAG, cytology) varied substantially from what is described in the literature with liver cirrhosis only accounting for over half the cases and malignancies contributed to quarter of cases. Current information related to the etiology of ascites should inform clinical practice particularly regarding the prioritization of diagnostic tests and setting up services.

SAT223

Sarcopenia is not associated with poor outcomes after transjugular intrahepatic portosystemic shunt insertion for refractory ascites

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Background and Aims: Sarcopenia is a common complication of end-stage chronic liver disease and is associated with adverse transplant waiting list and post-transplant outcomes. We undertook this study to evaluate whether sarcopenia was associated with hepatic encephalopathy (HE) or reduced transplant-free survival after transjugular intrahepatic portosystemic shunt (TIPSS) insertion.
Method: Adult cirrhotic patients undergoing TIPSS for diuretic refractory ascites or hepatic hydrothorax at King's College Hospital between 2010–2019 were retrospectively reviewed. Skeletal muscle index (SMI) was captured from CT imaging performed within 3 months of TIPSS using Sectra IDS7 image analysis software to calculate the cross-sectional area of abdominal skeletal muscle at the level of the third lumbar vertebrae and normalised to patient height (cm^2/m^2). Using pre-defined criteria, <50 cm^2/m^2 and <39 cm^2/m^2 were accepted cut-offs for the presence of sarcopenia. Demographic, biochemical, and radiological data were collected in addition to outcome data relating to episodes of early (<3 months) and late (>3 months) HE and transplant-free survival.
Results: 49 patients with diuretic refractory ascites were included in our analysis; 33 male, 16 female; mean age 56.2 +/– 19.8 years. Univariate analysis demonstrated no significant associations of biochemical data, organ severity scoring, ammonia or sarcopenia indices with the development of early or late HE. The majority (86%) of patients undergoing TIPSS for refractory ascites met radiological thresholds for sarcopenia. Late HE complicated 17/49 (35%) of TIPSS procedures. Ammonia (54.7 vs. 48.0 mmol/L, p = 0.50), MELD (11.9 vs. 11.9, p = 0.97) and baseline EEG evidence of mild HE (likelihood ratio 1.23, p = 0.64) were poor predictors of both early- and late hepatic encephalopathy; older patients were more likely to experience late hepatic encephalopathy (60.0 vs. 53.3, p = 0.023). SMI estimation showed good interobserver reliability (95%) and correlated well with estimated dry body mass index (BMI) as a marker of sarcopenia (pearson r = 0.651, p < 0.0001) but not ammonia (pearson r = 0.172, p = 0.33). Sarcopenia showed a trend towards an association with early HE (odds ratio 5.54, p = 0.167) but was not associated with late HE (odds ratio 1.18, p = 0.779) or transplant-free survival (p = 0.593).
Conclusion: Sarcopenia demonstrated a non-significant association with early HE but was not associated with either late HE or worse transplant-free survival and should not preclude consideration of TIPSS; this may reflect improvements in muscle mass and ammonia metabolism after TIPSS. Current modalities for predicting risk of HE post-TIPSS are poor and larger studies evaluating combined parameters in the assessment of advanced chronic liver disease are needed to improve prognostication in this area.

SAT224

Impact of acute decompensation on prognosis in patients with hepatocellular carcinoma

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Background and Aims: The most common hospital presentation of patients with cirrhosis is acute decompensation (AD). Among these patients, the occurrence of organ failure defines acute-on-chronic liver failure (ACLF), and it is characterized by high short-term mortality. However, little is known about the clinical features of AD during the long clinical course of hepatocellular carcinoma (HCC). The present study aimed to clarify the impact of AD on prognosis in patients with HCC.

Method: This retrospective study included data from our institutional database between 2011 and 2016. The study enrolled 617 consecutive patients initially diagnosed with HCC, and they were stratified into early, intermediate, and advanced stage groups (380, 121, and 116 patients, respectively).

Results: During a median follow-up of 35.9 months, 331 patients (early/intermediate/advanced: 177/82/72 patients) with AD were hospitalized. The AD incidence was greater in the intermediate/advanced group than in the early group (early: 7.9% at 1 y/21.2% at 3 y; intermediate: 27.8% at 1 y/54.9% at 3 y; advanced: 48.3% at 1 y/56.1% at 3 y; $p < 0.001$). AD during follow-up negatively affected long-term survival (free from AD vs. presence of AD; early: 95.8% vs. 88.9% at 1 y/89.9% vs. 67.0% at 3 y, $p < 0.01$; intermediate: 92.8% vs. 67.6% at 1 y/56.8% vs. 39.9% at 3 y, $p < 0.01$; advanced: 50.7% vs. 41.3% at 1 y/34.7% vs. 7.3% at 3 y, $p = 0.04$). Fifty-two patients (15.7%) (early/intermediate/advanced: 21 (11.8%)/19 (23.1%)/12 (16.6%) patients) with AD who presented ACLF at admission showed high 28-day mortality compared to those without ACLF (Non-ACLF) for all stages (Non-ACLF vs. ACLF; early: 16.7% vs. 52.4%, $p < 0.01$; intermediate: 20.6% vs.47.4%, $p = 0.04$; advanced: 30% vs. 66.7%, $p = 0.02$). However, there is no significance difference in 90-day mortality between Non-ACLF and ACLF patients in the intermediate (42.9% vs. 52.6%)/advanced (50% vs. 67%) group. In the intermediate/advanced stage, multivariate analysis showed that the CLIF-AD score (HR = 1.06 [95%CI: 1.01–1.12]; $p < 0.01$) and MELD score (HR = 1.10 [95%CI: 1.01–1.20]; $p < 0.01$) were independent predictors of 90-day mortality in non-ACLF patients. A prognostic model for 90-day mortality obtained by CART analysis indicated the following subpopulations with distinct prognoses: low risk (CLIF-AD score <53; 90-day mortality: 29%); intermediate risk (CLIF-AD score ≥53, MELD score <7/CLIF-AD score 53–62, MELD score ≥7; 90-day mortality: 35%–57%); and high risk (CLIF-AD score ≥63, MELD score ≥7; 90-day mortality: 76%).

Conclusion: Our findings indicate the prognostic importance of AD for mortality in patients with HCC. In patients with intermediate/advanced HCC, AD without ACLF might be associated with high 90-day mortality, and a simple CART algorithm involving the CLIF-AD score and MELD score can predict 90-day mortality.

SAT225

Serum cholinesterase is an independent predictor of hepatic encephalopathy, acute-on-chronic liver failure and mortality after transjugular intrahepatic portosystemic shunt insertion in patients with liver cirrhosis

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Background and Aims: Transjugular intrahepatic portosystemic shunt (TIPS) is an effective treatment for portal hypertension related complications. However, careful selection of patients eligible for TIPS is crucial and not indisputably established to date. Cholinesterase (CHE) has been suggested as a valuable marker for nutritional status as well as hepatic synthesis capacity. However, its potential as a predictor for the outcome after TIPS insertion has not been investigated in detail, so far. The aim of this study was to evaluate the potential value of CHE in patient selection for TIPS.

Method: All 201 consecutive cirrhotic patients providing informed consent and receiving a TIPS at Hannover Medical School between 2012 and 2018 were considered. One patient with missing CHE value was excluded. ROC curves were used to identify optimal cut-offs and log rank test to analyze survival. Role of CHE was analyzed with uni- and multivariate Cox Regression adjusting for MELD, TIPS indication (ascites or bleeding), age and portosystemic pressure gradient (PSG). Competing risk analysis was applied to evaluate hepatic encephalopathy (HE) or acute-on-chronic liver failure (ACLF) treating death as competing risk.

Results: Median age of the patients was 58 years and median MELD 11.9. TIPS indication was refractory ascites in about 75% and variceal bleeding in 25%. Overall, 34 patients (17%) died within 1 year after TIPS insertion. Those who died had a higher MELD ($p < 0.001$) and PSG ($p = 0.034$) as well as a significantly lower CHE at baseline ($p < 0.001$). Of note, other indicators of the hepatic synthesis capacity such as INR and albumin were not significantly different between both groups. A CHE of <2.49 kU/L was determined as optimal cut-off predicting 1-year mortality with a sensitivity of 85%, a specificity of 56% and a negative predictive value of 95% ($p < 0.001$, figure). Multivariate analysis revealed MELD (HR:1.18, $p < 0.001$) and CHE<2.49 kU/L (HR:5.14, $p = 0.001$) as only independent predictors for 1-year survival. A CHE<2.49 kU/L was also significantly associated with HE ($p = 0.012$) and ACLF ($p < 0.001$) development and remained statistical significant even after adjusting for MELD, TIPS indication, age and PSG in the multivariate analysis.

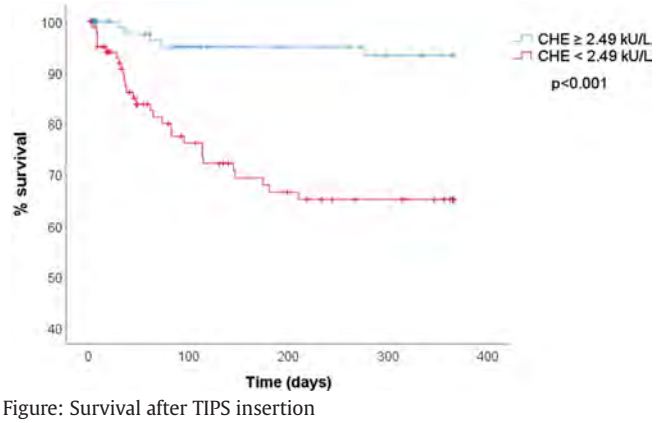

Figure: Survival after TIPS insertion

Conclusion: CHE is significantly associated with HE, ACLF and mortality after TIPS insertion. Therefore, it might be further evaluated as a novel, additional parameter when selecting patients for TIPS.

SAT226

Transjugular intrahepatic portosystemic shunt in cirrhotic elderly patients with refractory ascites - to do or not to do?

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Background and Aims: The management of cirrhotic patients with ascites is challenging, in particular at higher age when liver transplantation is restricted. Transjugular intrahepatic portosystemic shunt (TIPS) is an established therapeutic procedure for refractory ascites, but safety data in the older population are rare. The aim of this study was to evaluate the applicability and safety of TIPS insertion in elderly patients with decompensated liver cirrhosis and ascites.
Method: All consecutive cirrhotic patients receiving a TIPS for refractory ascites at Hannover Medical School between 2012 and 2018 were considered. Survival between patients <65 years (y) and ≥65 y was analyzed using the log-rank test. Multivariate Cox Regression was adjusted for MELD, sex and portosystemic pressure gradient. Periinterventional complications such as infections, hepatic encephalopathy (HE) and acute-on-chronic liver failure (ACLF) were compared using chi squared or Fisher's exact test. Propensity score matching was conducted to match TIPS patients ≥65 y 1:1 with those ≥65 y with refractory ascites treated with paracentesis.

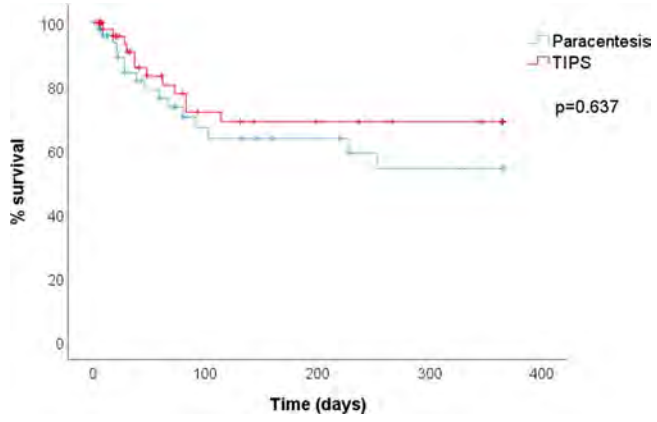

Figure: Survival of patients ≥65 y.

Results: Overall, 160 patients were included in the analysis with a median age of 59 y (n = 107 <65 y and n = 53 ≥65 y) and a median MELD of 12.6. Periinterventional course in those ≥65 y appeared slightly more complicated than in <65 y as reflected by a significantly longer hospital stay (p = 0.030), more ACLF episodes (21% vs. 10%; p = 0.044) and numerically more infections during hospital stay (26% vs. 17%; p = 0.153). Of note, no difference was observed in terms of HE. 28-day (d) mortality was similar between both groups (p = 0.350). In contrast, survival in the younger patients was significantly higher at 90d and numerically higher at 1 y (p = 0.029 and p = 0.171, respectively). Age ≥65 y remained an independent predictor for 90d mortality (HR:2.58; p = 0.028) in the multivariate analysis, while only MELD was associated with 1 y survival (HR:1.18; p < 0.001). Importantly, after matching for potential confounders 90d and 1 y survival was not inferior in elderly patients if treated with TIPS as compared to those managed with paracentesis (p = 0.796 and p = 0.637, respectively; figure).
Conclusion: TIPS in patients of higher age with refractory ascites appears to be slightly more complicated compared to younger individuals but well feasible and at least not inferior to paracentesis.

SAT227

Four weeks of aerobic and resistance training improves frailty in patients with liver cirrhosis-liver habilitation (Li-Hab) center outcome data

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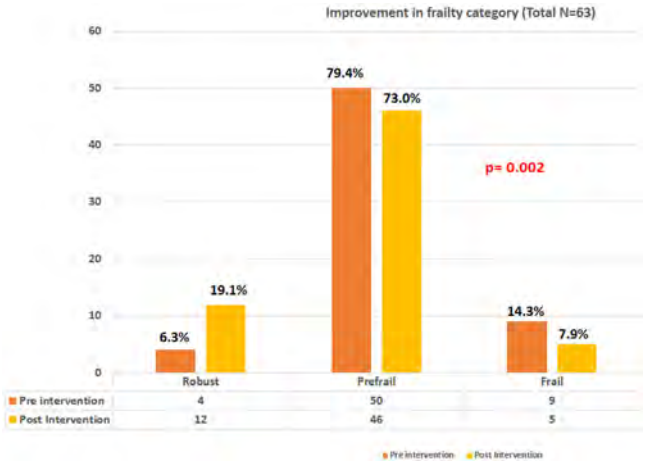
Background and Aims: Fatigue and reduced exercising capacity in cirrhotics results in physical inactivity and frailty which are associated with morbidity and mortality. A monitored exercise prescription (aerobic and resistance exercises) along with adequate nutrition are vital for muscle strength and performance. We evaluated feasibility and effect of structured exercise and nutritional programme on liver frailty index (LFI) and physical performance in cirrhotics.
Method: After a cardiopulmonary clearance, 96 consenting cirrhosis patients were enrolled into Li-Hab programme (LHP) in past 12 months. A 4-week LHP included 8 sessions of supervised exercise [treadmill walking and resistance exercises of major muscles with or without weights based on MRC (medical research council) scale; each for 30 minutes] as 2 sessions per week supervised by a physiotherapist, including at home. A diet comprising of 20–30 Kcal/Kg/day; and 1.2–1.5 g/Kg/day of protein as 6 divided meals including a pre-exercise and late evening protein supplements was prescribed. A complete physical and functional assessment was done [hand grip strength (HGS-Kg) by dynamometer, 6 minute walk test (6MWT-meters), gait speed (GS-meters second^{-1}) and LFI (HGS, chair rise and balance test)]. Frailty was categorised as LFI<3.2-robust; 3.3–4.5-prefrail; >4.5-frail. All assessments were repeated at the end of 8 sessions at 4 weeks.



Results: Out of 96, 63 (65.6%) patients [M-71.4%; Age-55.4 ± 10.8 yrs; CTP-6.4 ± 1.5; MELD-12.3 ± 3.7; BMI- 26.7 ± 4.6 Kg/m^2; aetiology (alcohol-23.8%, NASH-55.6%, others-20.6%); Child A:B:C (65.1%:30.2%:4.8%)] were 100% compliant with the LHP hence taken for pre-post analysis. There were no adverse events of LHP and no significant changes in body weight; however LFI improved by 6% (0.3)

(4.0 ± 0.58 to 3.7 ± 0.53; p < 0.001) 6MWT by 34 m (423 ± 105 to 457 ± 99; p < 0.001), GS by 0.13 m/s (0.97 ± 0.23 to 1.1 ± 0.2; p < 0.001), protein intake by 13 gm (62.3 ± 15.4 to 75 ± 12.6; p < 0.001) in all patients. Frailty category improved in 12 (19%) patients [8 became robust from pre-frail and 4 pre-frail from frail; Fig.1]

Conclusion: A structured exercise program is acceptable and feasible in cirrhosis patients. Four weeks of monitored exercise and nutrition program improves frailty, muscle strength and physical performance in these patients and is recommended for routine intervention.

SAT228

Effect of rivaroxaban on hypercoagulopathy risk factors in liver cirrhosis patients with nonvalvular atrial fibrillation

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Background and Aims: A number of studies have shown an increase in procoagulant risk in liver cirrhosis (LC) patients (ps). Long-term Direct Oral Anticoagulants (DOACs) are used for the treatment and prevention of thrombosis and thromboembolism, however, in LC, their use is limited. The aim of this study was to investigate the effect of DOACs drug Rivaroxaban on hypercoagulopathy risk factors in alcoholic (ALC) ps with nonvalvular atrial fibrillation (NVAF) and their safety profile.

Method: We analyzed 41 ALC ps with Child-Pugh class A cirrhosis and with NVAF (6 females/35 males; age, 51.3 ± 4.9 yr; body mass index (BMI), 34.7 ± 2.5 kg/m^2): 18 ps treated with Rivaroxaban 10 mg once daily in complex therapy in stroke prevention (I group), 23 ps treated with antiplatelet drugs (II group) for twelve months. ALC ps with Child-Pugh class B and C cirrhosis, with markers of hepatitis B and C viruses (HBV/HCV) were not included in the study. The results were compared with those of 20 healthy controls (group III; 4 females/16 males).

The diagnosis of LC was based on clinical, biochemical, ultrasound imaging and endoscopic findings, suggesting advanced liver disease with portal hypertension, Desmet's classification of chronic hepatitis in liver biopsy specimens (stage > 3) or liver stiffness assessed via elastography (F-score > 3). Factor VIII (FVIII), von Willebrand factor (vWF), antithrombin III (AT III), protein C, platelet-endothelial cell adhesion molecule-1, (PECAM-1), P-selectin, plasminogen activator inhibitor-1 (PAI-1), thrombin activatable fibrinolysis inhibitor (TAFI) plasma levels were measured by the immuno-assay method.

Results: Hypercoagulopathy was detected in 88.9% of ps in group I, 78.3% – of ps in II group. In ps with ALC ps with NVAF a statistically significant increase of FVIII (p = 0.008) and vWF (p = 0.001), PECAM-1 (p = 0.004), P-selectin (p = 0.002), PAI-1 (p = 0.001) and TAFI (p = 0.007) and decrease of AT III (p = 0.005), protein C (p = 0.002) plasma levels vs. group III were found.

After twelve months treatment with Rivaroxaban FVIII, vWF, PECAM-1, P-selectin, PAI-1 and TAFI plasma levels decreased in I group vs. group II (p < 0.05); AT III and protein C plasma levels in I group and group II were not significantly different (p > 0.05).

Ps in group I had no thrombotic or bleeding complications for 12 months, 1 (5.5%) patient had mild cytolytic syndrome, which was eliminated by silymarin without cancellation of rivaroxiban; 1 (4.3%) patient of group II had ischemic stroke, 1 (4.3%) – gastrointestinal bleeding.

Conclusion: Most ALC ps with Child-Pugh class A cirrhosis and with NVAF have a hypercoagulant state. Use of rivaroxaban for twelve months contributes to the reduction of hypercoagulopathy risk factors in ALC ps with Child-Pugh class A cirrhosis and with NVAF and has no serious side effects compared to antiplatelet drugs.

SAT229

Between rapid diagnosis and prediction of survival in minimal hepatic encephalopathy

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Background and Aims: Minimal hepatic encephalopathy (MHE) affect up to 80% of patients with liver cirrhosis. MHE predicts the onset of overt hepatic encephalopathy, is responsible for decreased health-related quality of life, and it is associated with an increased risk of motor vehicle accidents. The standard diagnosis method is Psychometric Hepatic Encephalopathy Score (PHES) but, recently, the EncephalApp Stroop test proved to be a valid diagnostic method. This study aims to assess the performance of the EncephalApp Stroop test in diagnosis MHE and to compare PHES and Stroop in predicting survival.

Method: A total of 148 consecutive patients with liver cirrhosis (LC) were enrolled between October 2017-July 2019, in a Romania tertiary health care center hospital. None of the patients showed clinical signs of overt hepatic encephalopathy at the inclusion. Patients were screened for MHE using PHES (n = 148) and Stroop (n = 143). The diagnosis of MHE was established with PHES score using the Romanian standardized scores, with a cut-off of <–4, and the Stroop result was expressed as time in seconds, consisting of the sum of 5 Stroop-off and 5 Stroop-on runs (the cut-off value for MHE was considered 245 sec).

Results: The etiology for liver cirrhosis was alcohol in 51 (34.5%) patients, viral in 84 (56.8%), and others in 13 (8.7%). The Child-Pugh class was A in 99 (66.9%) patients, B in 38 (25.7%), and C in 11 (7.4%), while the mean MELD-Na was 12.3 ± 5.29. MHE was identified in 59 (40%) patients.

The performance of Stroop was good, AUROC = 0.82 (95%C.I.: 0.74–0.89), p < 0.001 and an accuracy of 78%. Patients were followed-up on a median of 10.5 (22.5) months, and 16 deaths (10.8%) occurred during follow-up. Based on the PHES score, there is a significant difference in survival between the patients without HME (93.3%) and those with MHE (83.1%)(log-rank test, p = 0.05). If the Stroop test is used, there is no difference in survival between the patients without MHE (89.6%) and those with MHE (89.4%)(log-rank test, p = 0.8).

Conclusion: Although the Stroop test is a valid method for diagnosing MHE, it fails to predict survival as compared to the PHES score.

SAT230

Efficacy and safety of rivaroxaban in portal vein thrombosis in patients with liver decompensated cirrhosis

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Background and Aims: The use of rivaroxaban for portal vein thrombosis (PVT) in decompensated cirrhosis remains unknown. Here, we aimed to evaluate the pharmacokinetic characteristics, efficacy and safety of rivaroxaban for PVT in decompensated cirrhotic patients.

Method: Serial venous blood samples were collected after single-dose and multiple-dose of rivaroxaban administration to determine the plasma concentrations. We analysed the data of rivaroxaban with initial dose of 10 mg daily for PVT in cirrhotic patients between April

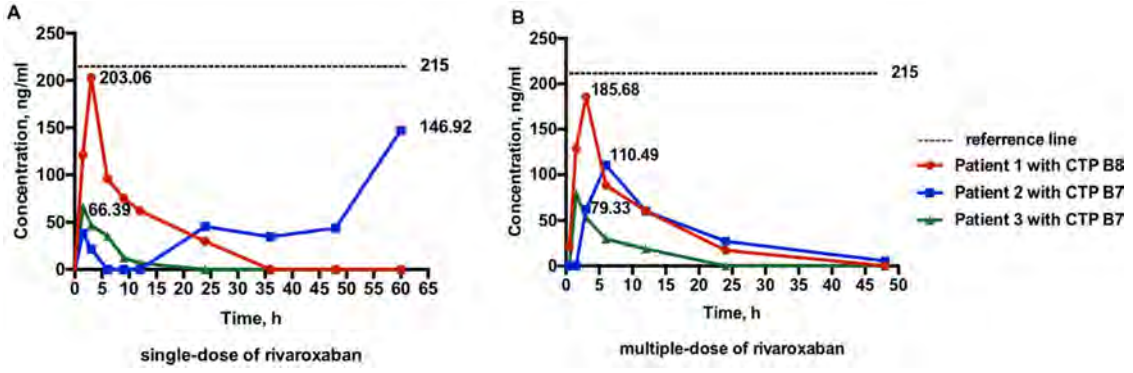

Figure: (abstract: SAT230): Single-dose (10 mg/d, A) and multiple-dose (10 mg/d, B) of rivaroxaban for PVT in three patients with decompensated cirrhosis (Child-Pugh B7-8) —reference line refers to Cmax of rivaroxaban (20 mg/d) at 2–4 h in non-cirrhotic patient.

2018 and Sep 2019 in our center. Regular imaging (abdominal CT or MRI) was performed to monitor the recanalization of PVT. Adverse events including bleeding episodes were recorded during anticoagulation treatment.

Results: 1. One patient with Chid-Pugh B8 had maximum concentrations (Cmax) with 203.06 ng/ml and 185.68 ng/ml at 3 h after single-dose and multi-dose of rivaroxaban respectively. The Cmax in single-dose and multiple-dose of two patients with Child-Pugh B7 were 146.92 ng/ml at 60 h, 66.39 ng/ml at 1.5 h and 110.49 ng/ml at 6 h, 79.33 ng/ml at 1.5 h respectively. **2.** A total of six patients with Child-Pugh B (7–9) enrolled. The median follow-up under anticoagulation therapy was 9.7 months (rang 2.8–17.9 months). Partial recanalization was achieved in 4 patients (66.7%) with a median time of 4.8 months, but two patients with lower Cmax had thrombosis progression at 12 m. **3.** Two bleeding episodes (minor gastrointestinal bleeding and gingival bleeding), two hepatic encephalopathy (Grade II or more) were observed. One patient had a significantly decreased platelet. **4.** Compared with baseline, no significant difference in Child-Pugh score, MELD score, hepatic and renal function, platelet and prothrombin time at 3 m, 6 m and 12 m during rivaroxaban treatment were observed.

Conclusion: Rivaroxaban may provide a promising benefit for PVT in decompensated cirrhotic patients, and need to be further studied.

SAT231

Test-retest reliability of hepatic venous pressure gradient: a study in 215 patients from the control arms of 17 randomized controlled trials

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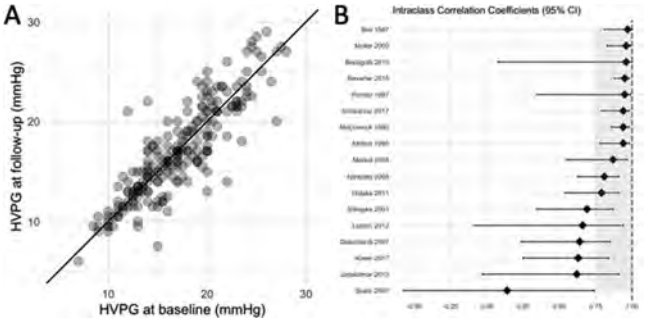
Background and Aims: Portal hypertension (PH) is a major driver for cirrhosis complications. Portal pressure is estimated in practice by the hepatic venous pressure gradient (HVPG). The assessment of HVPG changes has been used for drug development in PH. Moreover, there is increasing interest in wider use of HVPG as a clinical outcome measure in RCTs for the treatment of cirrhosis. This requires a thorough understanding of the test-retest reliability of HVPG. This study aimed at quantifying the test-retest reliability of HVPG in the specific context of RCTs for the treatment of PH in cirrhosis.

Method: We performed a systematic search of published RCTs in patients with cirrhosis reporting individual patient-level data of HVPG at baseline and after an intervention, and that included a placebo or untreated control arm. Baseline and follow-up HVPG in the control groups were extracted after digitizing the plots. Test-retest reliability was estimated by the intraclass correlation coefficient (ICC). Pooled ICC and potential associations with study characteristics were estimated with linear mixed models (patient and study as random effects). We considered ICC > 0.75 as excellent as recommended for measures with physiological variability.

Results: Seventeen trials including a total of 215 patients in the placebo/untreated groups had plots with legible individual HVPG changes. Time range between HVPGs was 20 min to 730 days. Fig. A shows the association between baseline and follow-up HVPGs, and Fig. B the ICCs of individual studies. 18% and 8% of the patients showed a ≥10% and ≥20% response, respectively. 11/17 studies showed excellent reliability (>0.75) of repeated HVPGs, and 5 showed moderate reliability. Only one study showed poor reliability (ICC: 0.14). In that study, a wedged catheter was used for HVPG measurement (as opposed to balloon catheter in the other 16 studies). Pooled ICC was excellent (0.88). We did not find an association between reliability and proportion of patients with alcohol-related liver disease, compensated vs decompensated cirrhosis, multicentric vs single-center studies, year of publication or time between measurements.



Conclusion: We show in this study that, in the context of RCTs, test-retest reliability of HVPG is excellent. We provide quantitative information on the range of expected reliability parameters, that will be useful for sample size calculation and results' interpretation in trials with HVPG as an outcome measure.

SAT232

The survival effect of sarcopenia in patients with cirrhosis undergoing transjugular intrahepatic portosystemic shunt: a single-center review

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Background and Aims: Sarcopenia is common in patients with cirrhosis and is associated with increased mortality. Placement of

Variable	OR	Interval	P value	Multivariate analysis	CI	P value
Sarcopenia	2.556	1.381-4.728	0.003	1.88	1.056-3.378	0.032
BMI	0.985	0.947-1.024	0.449	0.994	0.953-1.036	0.763
MELD	1.093	1.036-1.153	0.001	1.089	1.025-1.157	0.006

Figure: (abstract: SAT232)

transjugular intrahepatic portosystemic shunt (TIPS) is frequently utilized in cirrhotic patients with hepatic decompensation. No studies have evaluated the association between the presence of sarcopenia and its effect on mortality after TIPS. The purpose of this study was to investigate the post TIPS mortality in patients with sarcopenia.

Method: We conducted a single-centre retrospective study of 305 patients with cirrhosis who underwent TIPS between 2010 and 2015. Psoas muscle index at the third lumbar vertebra (PMI) was measured by computed tomography adjusted by height. Sarcopenia was defined as a PMI less than the 25th percentile of the study population stratified by gender as previously described. We conducted univariate and multivariate analysis to identify the association between sarcopenia and post-TIPS mortality.

Results: Overall 184 (60.3%) patients received TIPS for refractory ascites, 97 (31.8%) patients received TIPS for oesophageal variceal (EV) bleeding and 24 (7.9%) for other indications. The mean age was 63.88 ± 9.86 years old. Sarcopenia was present in 67 (22%) of patients. Median MELD scores for the Sarcopenic and non-Sarcopenic groups were 13.25 ± 3.98 and 12.98 ± 5.06 ($p = 0.602$) respectively. BMI was higher for the non-Sarcopenic patients compared to those with Sarcopenia, 29.13 ± 6.27 and 25.36 ± 6.37 ($p < 0.001$), respectively. Average PMI was lower in the Sarcopenic group compared to those without Sarcopenia, 2.66 ± 0.47 vs 4.94 ± 1.28 ($p < 0.001$). Patients with sarcopenia had higher mortality rate at 1 year as compared to patients without sarcopenia (38.8% vs 25.2%, $p < 0.05$). Multivariate analysis after adjusting MELD and BMI, patients with sarcopenia had higher odds of mortality comparing to patients without sarcopenia (odds ratio [OR]: 1.88, 95%; confidence interval [CI]: 1.056–3.378). However, no statistically significant differences were found between sarcopenia and long term (3-year and 5-year) mortality.

Conclusion: In cirrhotic patients with sarcopenia who underwent TIPS, there was increased mortality at 1 year but not beyond. Future studies are needed to investigate the impact of post-TIPS nutrition optimization in this patient population.

SAT233

Comparison of MELD, MELD-Na and MELD-sarcopenia in predicting mortality in patients with cirrhosis undergoing transjugular intrahepatic portosystemic shunt

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Background and Aims: The Model for End-Stage Liver Disease (MELD) score was developed to predict the mortality after transjugular intrahepatic portosystemic shunt (TIPS). Limitations to the MELD in predicating post TIPS mortality have led to subsequent derivations such as MELD-Na and MELD-Sarcopenia. However, few studies have compared these MELD modifications in predicting post TIPS mortality. The purpose of this study was to compare the various derivations of the MELD formula in patients undergoing TIPS.

Method: At our medical centre, 305 consecutive patients underwent TIPS placement from Jan 2010 to Dec 2015. MELD, MELD-Na and MELD-sarcopenia scores were calculated for each patient. MELD-Sarcopenia was calculated as MELD+10.35 × Sarcopenia as previously reported. Receiver operating characteristic (ROC) Curves were used to compare the MELD, MELD-Na and MELD- Sarcopenia scores and determine their accuracy in predicting the mortality after TIPS for various indications.

Results: Overall 184 (60.3%) patients received TIPS for refractory ascites, 97 (31.8%) patients received TIPS for oesophageal variceal (EV) bleeding and 24 (7.9%) for other indications. The mean age was 63.88 ± 9.86 years old. The mean MELD score was 13.04 ± 4.83 and mean MELD-Na score was 15.75 ± 5.64. Sarcopenia was present in 67 (22%) of patients. The mean MELD-Sarcopenia score was 23.40 ± 4.84. Mortality after TIPS was 28.20% at 1 year and 54.75% at 5 years. Based upon ROC curves, none of the MELD derivations (MELD-Na, MELD-sarcopenia) delineated themselves as being a better predictor of mortality post TIPS at 1 and 5 years as compared to the MELD score (AUC of 0.65, 0.65 vs 0.63 at 1 year and 0.60, 0.60 vs 0.61 at 5 years). Regarding indications of TIPS placement, the MELD score and its derivations showed better prediction of mortality at 1 and 5 years in patients receiving TIPS for EV bleeding compared to patients receiving TIPS for ascites ($P < 0.05$).

Conclusion: There is no difference between MELD score and its related modifications (MELD-Na and MELD-Sarcopenia) in predicting mortality in patients post TIPS. However, when evaluating the indications for TIPS, the scores may be useful. Prospective studies are needed to confirm our observations.

SAT234

Empirical carbapenem versus third-generation cephalosporin treatment for spontaneous bacterial peritonitis: a multicenter study

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Background and Aims: Third-generation cephalosporin (TGCs) is currently recommended as the first-line empirical antibiotic for spontaneous bacterial peritonitis (SBP). However, recent studies suggest that antibiotics against multidrug-resistant organisms (e.g.,

carbapenem) may be necessary, particularly for nosocomial SBP. This study aimed to evaluate whether carbapenem is superior to TGC for SBP.

Method: This study retrospectively examined consecutive SBP patients at seven referral centers in Korea. The primary outcome was in-hospital mortality and secondary outcomes included 3-month mortality.

Results: A total of 827 patients with SBP were included; 253 (30.6%) were culture-positive. The in-hospital mortality rate was higher in culture-positive SBP patients than in culture-negative patients (31.6% vs. 23.7%, P = 0.02). Among culture-positive SBP patients, 100 (39.5%) had TGC-resistant bacterial infection. As initial empirical antibiotics, 632 patients (76.4%) received TGCs and 86 (10.4%) received carbapenem. Among the entire study cohort, there was no significant difference in in-hospital mortality between the TGC and carbapenem groups in multivariable analyses (adjusted odds ratio [aOR], 0.80; 95% confidence interval [CI], 0.46–1.42; P = 0.45). However, in patients with a high CLIF-SOFA score (≥7, n = 301), the administration of carbapenem as an empirical antibiotic was independently associated with significantly lower in-hospital mortality (aOR, 0.42; 95% CI, 0.19–0.91; P = 0.03). In contrast, in-hospital mortality was comparable between carbapenem and TGC groups in patients with a low CLIF-SOFA score (n = 417; aOR, 1.53; 95% CI, 0.64–3.67; P = 0.34).

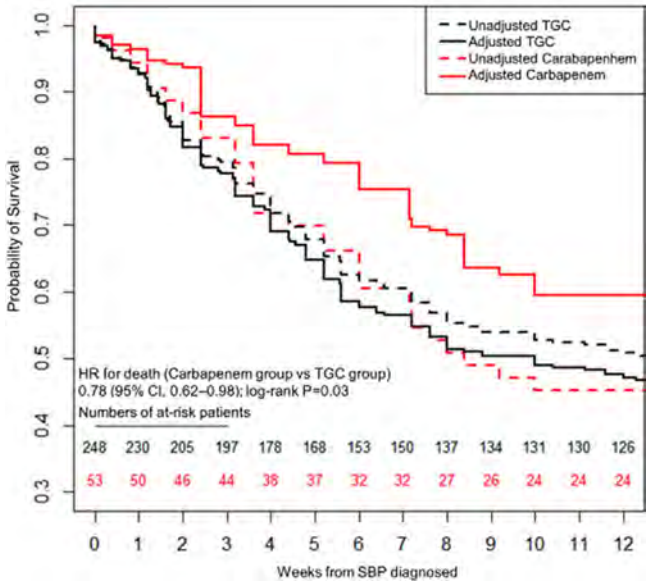

Figure: Kaplan-Meier estimates of overall survival in SBP patients with a high CLIF-SOFA score

Conclusion: In the overall SBP cohort, empirical carbapenem treatment failed to improve in-hospital mortality versus TGCs. However, among critically ill patients with a high CLIF-SOFA score, empirical carbapenem treatment was significantly associated with lower in-hospital mortality versus TGCs.

SAT235

Early albumin improves survival in cirrhotic patients on diuretic therapy who develop significant acute kidney injury: real-world evidence in the United States

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Background and Aims: Acute kidney injury (AKI) is diagnosed in 20% to 50% of patients hospitalized with cirrhosis. AKI is associated with poor prognosis and high mortality among this population, especially in AKI stage 3. Albumin infusion is an essential component for the evaluation and management of renal dysfunction in cirrhotic patients. The aim of this study is to examine the impact of albumin infusion on mortality in hospitalized cirrhotic patients on diuretic therapy, who develop significant AKI during their hospital stay.

Method: We utilized a nationwide Electronic Health Record dataset (Cerner Health Facts(R)) to extract real-world data on adult patients (> = 18 years old) with cirrhosis, admitted from January 1, 2009, through April 30, 2018. Further, we only included patients with AKI stage 3 who received diuretics before (including a 30-day lookback period) or on the same day as when they developed any AKI. International Classification of Diseases (ICD-9/10) codes were used to identify cirrhosis and other diagnostic information. We reported significant AKI as stage 3 based on the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. The Model for End-stage Liver Disease Sodium (MELD-Na) score was calculated for each patient visit at baseline using laboratory data. We used multivariable logistic regression to assess the relationship between albumin infusion and mortality.

Results: We identified 23,745 unique visits for patients with cirrhosis and AKI of any stage, out of which 609 visits met the inclusion criteria. Albumin was infused within 24 hours of admission ('early albumin') in 36% and after 24 hours in 42%, while it was not administered in 22%. MELD-Na was higher at presentation in early albumin cases than late- or no-albumin cases (mean 29.5 and 23.6). Unadjusted mortality was lower in patients receiving early albumin (33.5%) than late or no albumin (38.9%). Adjusted analysis revealed that odds of mortality were lower for patients who received early albumin as compared to patients who received late or no albumin (OR 0.52, 95% CI 0.32–0.87, p = 0.013).

	Early Albumin (< = 24 hrs.) N = 218	Late (>24 hrs.)/ No Albumin N = 391	Standardized Mean Difference
	N (%)	N (%)	
Male	142 (65.1%)	224 (57.3%)	−0.162
Unadjusted Mortality	73 (33.5%)	152 (38.9%)	−0.112
	Mean (SD)	**Mean (SD)**	
Age	59.1 (12.0)	59.0 (12.8)	0.007
Baseline MELD-Na	29.5 (8.1)	23.6 (8.9)	0.688
Baseline Charlson Comorbidity Index	9.2 (4.0)	8.9 (3.8)	0.083

Conclusion: These real-world data indicate that early use of albumin has a mortality benefit in hospitalized cirrhotic patients who develop AKI stage 3. Following the established guidelines of using albumin infusion early in this patient population may lower the likelihood of death. The data also suggest that, in many cases, albumin is administered to patients late in their hospital stay, presumably when prior therapies have failed.

SAT236

Test-retest reliability of hepatic venous pressure gradient: a study in 215 patients from the control arms of 17 randomised controlled trials

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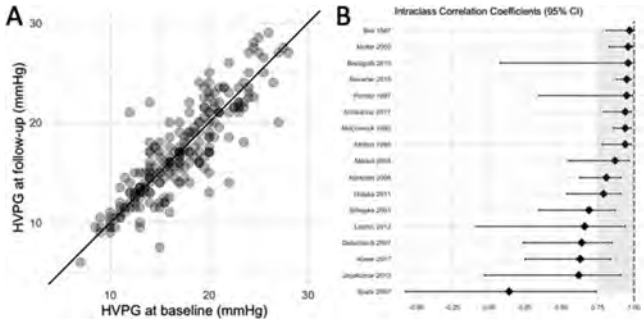
Background and Aims: Portal hypertension (PH) is a major driver for cirrhosis complications. Portal pressure is estimated in practice by the hepatic venous pressure gradient (HVPG). The assessment of HVPG changes has been used for drug development in PH. Moreover, there is increasing interest in wider use of HVPG as a clinical outcome measure in RCTs for the treatment of cirrhosis. This requires a thorough understanding of the test-retest reliability of HVPG. This

study aimed at quantifying the test-retest reliability of HVPG in the specific context of RCTs for the treatment of PH in cirrhosis.
Method: We performed a systematic search of published RCTs in patients with cirrhosis reporting individual patient-level data of HVPG at baseline and after an intervention, and that included a placebo or untreated control arm. Baseline and follow-up HVPG in the control groups were extracted after digitizing the plots. Test-retest reliability was estimated by the intraclass correlation coefficient (ICC). Pooled ICC and potential associations with study characteristics were estimated with linear mixed models (patient and study as random effects). We considered ICC>0.75 as excellent as recommended for measures with physiological variability.
Results: Seventeen trials including a total of 215 patients in the placebo/untreated groups had plots with legible individual HVPG changes. Time range between HVPGs was 20 min to 730 days. Fig. A shows the association between baseline and follow-up HVPGs, and Fig. B the ICCs of individual studies. 18% and 8% of the patients showed a ≥10% and ≥20% response, respectively. 11/17 studies showed excellent reliability (>0.75) of repeated HVPGs, and 5 showed moderate reliability. Only one study showed poor reliability (ICC: 0.14). In that study, a wedged catheter was used for HVPG measurement (as opposed to balloon catheter in the other 16 studies). Pooled ICC was excellent (0.88). We did not find an association between reliability and proportion of patients with alcohol-related liver disease, compensated vs decompensated cirrhosis, multicentric vs single-center studies, year of publication or time between measurements.



Conclusion: We show in this study that, in the context of RCTs, test-retest reliability of HVPG is excellent. We provide quantitative information on the range of expected reliability parameters, that will be useful for sample size calculation and results' interpretation in trials with HVPG as an outcome measure.

SAT237

Prognosis of alcoholic or viral B/C cirrhosis according to ABO blood group: results of abocirralvir, from CIRRAL and ANRS CO12 CirVir cohorts

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Background and Aims: Non-O blood group (Non-O Gp) promotes deep vein thrombosis and venous thromboembolism recurrence in general population. Non-O Gp has also been associated with an increased risk of liver fibrosis in hepatitis C and hepatocellular carcinoma (HCC). The mechanism could be microthrombotic due to the decrease of ADAMTS 13 activity resulting in an increase of procoagulant factors VIII and Willebrand. These kinds of coagulation alterations are observed in case of cirrhosis. The aim was to evaluate the influence of Non-O Gp on the prognosis of alcoholic or viral cirrhotic patients.
Method: This is an observational study from CIRRAL et CIRVIR, 2 prospective cohorts of alcoholic and virological Child-Pugh A cirrhotic patients. The main criterion was the cumulated incidence of complications at 3 years with 2 composite criteria: « **Decompensation** » defined as at least one sign among: ascites, hydrothorax, encephalopathy, portal hypertension bleeding, bilirubin >45 umol/l, spontaneous bacterial peritonitis and « **Disease Progression** » including a « Decompensation » or « the occurrence of one or more parameters » : PT < 45%, albumin <28 g/l, Child-Pugh aggravation, hepatorenal syndrome, non tumoral portal vein thrombosis (NTPT), hepato-pulmonary syndrome, or pulmonary arterial hypertension.

Table 1: (abstract: SAT238): noninvasive criteria for ruling out high-risk varices.

	APP score <0.24				
Variable	Training cohorts (221)	Validation cohorts (113)	ALB<3.6 and PLT <120	PLT >150 or MELD = 6	p-value
EGD Spared	56.6% (125/221)	51.3% (59/113)	31.7% (70/221)	27.6% (61/221)	<0.0001
HRV miss	4.8% (6/125)	1.7% (1/59)	1.4% (1/70)	1.6% (1/61)	0.42
Low risk varices miss	(14.4%) 18/125	(11.7%) 7/59	(10.0%) 7/70	(8.2%) 5/61	0.75
NPV	95.2%	98.3%	98.6%	98.3%	0.30

Results: 1787 cirrhotic patients (pts) (519 alcoholic and 1268 viral C or B), median age 56 years, 67.7% male, have been followed during a median of 64 months (at least 3 years for 79,4% of patients), 60% were Non-O Gp and 40% Gp O. The cumulated incidence of complications at 3 years was respectively 32.1% in Non-O Gp (46.1% of pts), and 29.4% (42.5% of pts) in Gp O (p = 0.20). Among these complications, in the Non-O Gp, the cumulated incidences of NTPT and HCC were respectively 3.2% and 9.2% at 3 years. In the Gp O, theses incidences were 3.4% (p = 0.63) and 7.7% (p = 0.51). The probability of **Decompensation** or **Disease Progression** at 3 years did not differ according to blood group. At 3 years the cumulated incidence of **Decompensation was** 8.3% in the Non-O Gp (14.2% of pts) and 7.3% in the Gp O (12.2% of pts) (p = 0.28). At 3 years the cumulated incidence of **Disease Progression** was 22.1% in the Non-O Gp (33.1% of pts) and 20.7% in the Gp O (29.9% of pts) (p = 0.25). The 3 years mortality rate was similar in both groups: 183 (17.1%) patients of Non-O Gp and 124 (17.3%) patients of Gp O. Death was related to liver disease in 54.6% of cases with 25% due to HCC. At 3 years the overall survival was 92.6% in the Non-O Gp and 93.6% in the Gp O (p = 0.90). Platelets, albumin and bilirubin were prognostic factors related to most of the events.
Conclusion: Despite its thrombotic role in general population, Non-O group is related neither to the risk of non tumoral portal vein thrombosis, nor to the risk of hepatocellular carcinoma, nor to the risk of disease progression in well compensated cirrhotic patients.

SAT238
Development and validation of a risk scoring system for screening high-risk varices
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Background and Aims: to create and validate an easy-to-use risk score system based on routine laboratory and routine liver doppler ultrasonography to accurately identify high-risk varices and spare esophagogastroduodenoscopy (EGD) in patients with hepatitis B virus (HBV) related compensated advanced chronic liver disease (cACLD).
Method: this was a single-center retrospective study. The training cohorts included 221 patients and validation cohorts included 113 patients. All patients were diagnosed with HBV related cACLD, and had routine biochemical examination, liver doppler ultrasonography and esophagogastroduodenoscopy (EGD) results.
Results: in training cohorts, the prevalence of HRV was 29.5%. a large proportion of patients with Child-Turcotte-Pugh A (94.1%). Within the multivariable logistic regression analysis, ALB (OR: 0.832; 95% confidence index (CI): 0.773–0.895; p < 0.0001), PLT (OR: 0.975, 95% CI: 0.964–0.986; p < 0.0001) and PVD (OR: 1.402; 95% CI: 1.152–1.706; p = 0.001) were independent risk factors for presence of HRV. The following risk score was created: logistic (P) = 4.780 + 0.338(PVD) –0.025(PLT)–0.184(ALB), which was named as albumin-platelet-portal vein diameter varices risk score (APP score). APP score <0.24, resulted in negative predictive value (NPV) were 95.2%. Within training cohort, 125 of 221(56.6%) patients met the new criteria of APP score <0.24. In validation cohort, 59 of 113 (51.3%) patients met the APP score <0.24. Several previous reported routine biochemical based criteria also analyzed in training cohort. 70 of 211 (31.7%) patients met the criteria (ALB<3.6 g/L or PLT<120 × 109 cells/L). PLT>150 × 109 cells/L or MELD = 6 can spare 61 of 221(27.6%) EGD screenings. The number of spared EGD with APP score in training cohort and validation cohort was larger than previous reported criteria(P < 0.0001), had equivalent HRV miss rate (P = 0.42), low risk varices miss rate (P = 0.75) and NPV (P = 0.30) (Table 1).
Conclusion: APP score <0.24 is a potential model for safely screening HRV in patients with HBV related-cACLD.

SAT239
Effect of rifaximin or norfloxacin on hepatic venous pressure gradient in patients with cirrhosis: a systematic review and meta-analysis
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Background and Aims: Translocation of intestinal bacteria or of bacterial products is thought to worsen chronic liver disease and portal hypertension. The effects on hepatic venous pressure gradient (HVPG) of non- or poorly-absorbable antibiotics commonly used for intestinal decontamination in cirrhosis are debated. This systematic review analyzes the effects of rifaximin or norfloxacin on HVPG and on markers of bacterial translocation and proinflammatory cytokines.

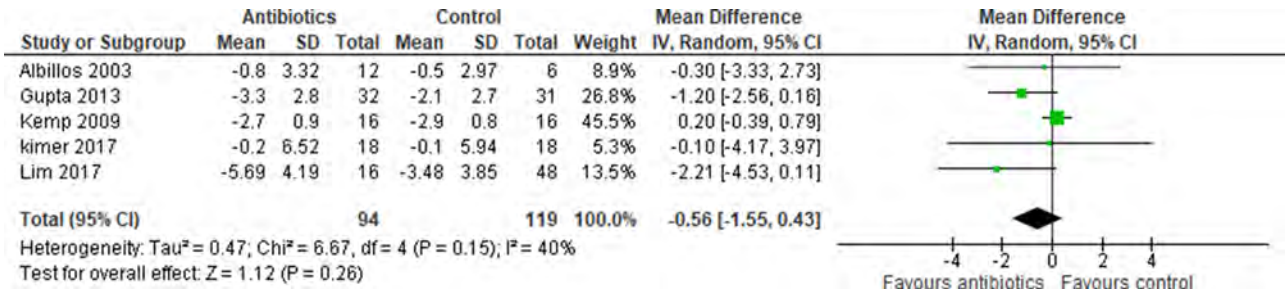

Figure: (abstract: SAT239)

Method: We performed a systematic search of the MEDLINE, EMBASE and SCOPUS databases (in English, up to December 2018). Two authors independently extracted randomized clinical trials (RCT) involving patients with cirrhosis and portal hypertension, assessing the effect of antibiotics (rifaximin or norfloxacin) vs control (placebo or no medication) on HVPG. Some studies associated non-selective beta-blocker (NSBB) in both the actively treated and the control arm. Pooled analyses were based on random-effects models, heterogeneity was assessed by Cochran's Q, I2 statistic and subgroup analyses. We used the Cochrane Collaboration's tool for risk of bias assessment.
Results: Five studies (215 patients) were included; the majority had low quality for control of bias. HVPG changes after antibiotics (norfloxacin or rifaximin) or control were similar. The summary mean absolute difference in HVPG was - 0.56 mmHg (95% CI: −1.55–0.43; p = 0.26), with moderate heterogeneity (I2 = 40%) (Figure), which disappeared after pooling RCTs with longer therapy (60–90 days). In the latter group, antibiotics were given in combination with NSBB and the observed reduction in HVPG was greater (mean difference −1.46 mmHg; 95% CI: −2.63 – −0.28; p = 0.01) than in controls (NSBB alone or plus placebo). Lipopolysaccharide-binding protein (LBP) was reported in 3 studies, and significantly decreased with antibiotics in all; levels of interleukin-6 and tumor necrosis factor alpha decreased significantly in 2/3 studies.
Conclusion: Rifaximin or norfloxacin did not significantly reduce HVPG in patients with cirrhosis and CSPH in the available studies. This conclusion is partly limited by heterogeneous population, small numbers and low quality of the studies. Studies using antibiotic plus NSBB for longer periods showed a significantly greater decrease in HVPG as compared to NSBB alone. Whether antibiotics combined to NSBB improve portal hypertension should be confirmed in an appropriately designed RCT

SAT240

Repeated versus single treatment of esophageal variceal ligation after esophageal variceal bleeding

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Background and Aims: International guidelines recommend repeated esophageal variceal ligation (EVL) for treatment of esophageal variceal bleeding. However, due to patient compliance and complications of repeated EVL procedure, many physicians perform single EVL treatment after varix bleeding. We aimed to compare the risk of variceal re-bleeding after repeated EVL versus single EVL.
Method: This retrospective study included consecutive patients who underwent initial esophageal variceal ligation (EVL) for the first esophageal variceal bleeding. Primary endpoint was the recurrence of variceal bleeding and uni-/multi-variate analyses were conducted to find independent predictors.
Results: A total of 210 patients were included: 133 in the repeated EVL group and 77 in the single EVL group. During follow-up duration (median = 46.5 months), 17 (12.8%) in the repeated EVL group and 36 (46.8%) in the single EVL group developed re-bleeding (P < 0.01 by log-rank test). However there were no difference of overall survival between the two groups (P = 0.05). Multivariate analysis showed that the single EVL group compared to the repeated group (adjusted hazard ratio [aHR] = 3.372, 95% confidence interval [CI] = 1.824–6.234, P < 0.001) was the only independent risk factor after adjustment for alcohol etiology (HR = 3.370, 95% CI = 1.717–6.618, P < 0.001), combined gastric varix (HR = 1.333, 95% CI = 1.250–9.612, P = 0.017) and high MELD score (HR = 2.379; 95% CI = 1.192–4.748; P = 0.014).
Conclusion: Repeated EVL after esophageal varix bleeding can improve re-bleeding. However, there was no difference in overall survival. Further randomized control studies are needed.

Non-invasive assessment of liver disease except NAFLD

SAT241

Serum gamma-glutamyl transpeptidase as a simple and useful indicator for predicting significant fibrosis in patients with chronic hepatitis B

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Background and Aims: Assessing the stages of liver fibrosis is critical in guiding the treatment of chronic hepatitis B (CHB). The gamma-glutamyl transpeptidase (GGT) was reported to be associated with the severity of liver diseases. We aimed to investigate the association between GGT and the severity of liver fibrosis in CHB.
Method: Six hundred eighty-three treatment-naïve CHB patients who underwent liver biopsy were enrolled from two medical centers. Liver histology was evaluated using the Scheuer classification system. The diagnostic accuracy was evaluated by the area under the receiver operating characteristic curve (AUROC).
Results: The GGT level showed an increasing trend with fibrosis stages in CHB patients. The GGT level was positively correlated with the stages of liver fibrosis in entire CHB patients (r = 0.346, p < 0.001), HBeAg positive CHB patients (r = 0.438, p < 0.001) and HBeAg negative patients (r = 0.307, p < 0.001). GGT was an independent factor for predicting significant fibrosis (S ≥ 2) in the entire CHB patients and HBeAg positive patients, but not in HBeAg negative patients. The AUROCs of GGT for predicting significant fibrosis were 0.658 (95%CI 0.6148 to 0.7016), 0.703 (95%CI 0.6453 to 0.7603) and 0.628 (95%CI 0.5616 to 0.6938) in entire CHB patients, HBeAg positive and HBeAg negative CHB patients, which was comparable with aspartate transaminase (AST) to PLT ratio index (APRI) (p > 0.05) and fibrosis-4 score (FIB-4) (p > 0.05).
Conclusion: The GGT level was positively correlated with the severity of liver fibrosis in CHB patients. The GGT level alone showed similar diagnostic accuracy for significant fibrosis in CHB patients as compared to APRI and FIB-4.

SAT242

The predictive value of MRI-based markers of liver disease on clinical outcomes in patients with cirrhosis

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Background and Aims: Non-invasive risk stratification for liver-related outcomes is important for the management of patients with cirrhosis. This prospective cohort study explores the ability of magnetic resonance imaging (MRI)-based markers of a.) liver fibrosis (liver cT1); b.) portal hypertension (spleen extracellular volume fraction (ECV)); and c.) liver function (percentage reduction in liver T1 with gadoxetic acid (%rT1)) to predict liver-related outcomes.

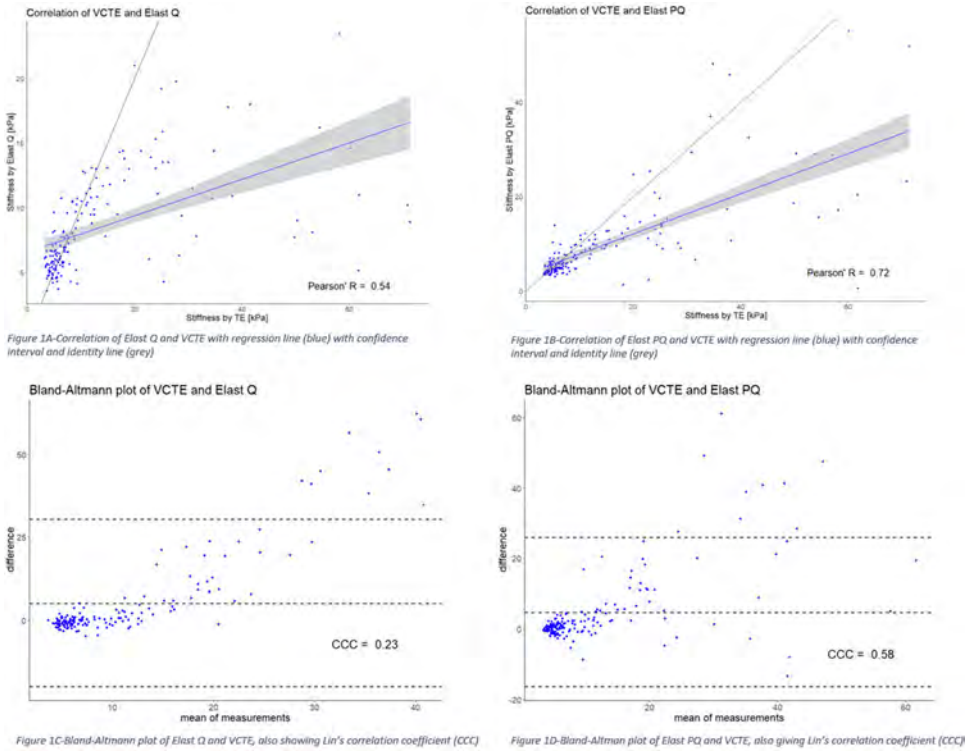

Figure 1A-Correlation of Elast Q and VCTE with regression line (blue) with confidence interval and identity line (grey)

Figure 1B-Correlation of Elast PQ and VCTE with regression line (blue) with confidence interval and identity line (grey)

Figure 1C-Bland-Altmann plot of Elast Q and VCTE, also showing Lin's correlation coefficient (CCC)

Figure 1D-Bland-Altman plot of Elast PQ and VCTE, also giving Lin's correlation coefficient (CCC)

Figure: (abstract: SAT243)

Method: One hundred and thirty-five patients with cirrhosis of mixed aetiologies were followed up by telephone consultation and medical record review for ≥1 year following MRI with gadoxetic acid administration, clinical, blood and transient elastography assessments. Time to first development of a composite endpoint comprising new variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatocellular cancer, liver transplantation or liver-related death was recorded. The association of MRI and other non-invasive liver disease markers with the composite endpoint was assessed by Kaplan Meier and Cox regression analyses.
Results: The cohort of median age 61 (IQR 54–8) years comprised 73% males and 74% with compensated advanced chronic liver disease (cACLD). During follow up of median 571 (IQR 432–634) days, 28 (21%) patients reached the composite endpoint. Spleen ECV >0.36 and %rT1 <55.05% were associated with reduced endpoint-free survival (both $p < 0.001$). Liver cT1 (HR 1.004, $p = 0.026$), spleen ECV (HR 1.068, $p = 0.001$) and %rT1 (HR 0.922, $p < 0.001$) were predictive of the composite endpoint in univariate analysis. Of the MRI markers, %rT1 ($p = 0.015$) remained a significant predictor of the composite endpoint in multivariable analysis, together with bilirubin ($p = 0.001$), sodium ($p = 0.014$), Child Pugh score ($p = 0.005$), MELD ($p = 0.004$) and APRI ($p = 0.001$).
Conclusion: MRI-based markers of liver fibrosis, portal hypertension and liver function are predictive of liver-related outcomes. In particular, %rT1 adds prognostic benefit to clinical and serum-based markers.

SAT243

Elast q - 2D shear wave liver elastography correlates well with vibration controlled transcient elastography in patients with different etiologies of chronic liver disease

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Background and Aims: Two dimensional (2D-SWE) and point shear wave (pSWE) elastography modules implemented on high-end ultrasound machines are increasingly used for screening of liver disease. As compared to vibration-controlled transient elastography (VCTE), ultrasound-based elastography quantification (ElastQ) allows fibrosis assessment in a larger region of interest.
Method: In this prospective multicenter study, we acquired paired liver stiffness measurements (LSM) by VCTE and 2D-SWE (ElastQ) and pSWE (ElastPQ) using the Philips EPIQ7 system. We applied WFUMB quality criteria (ElastQ: median of 5, VCTE and Elast PQ: median of 10 acquisitions, respectively; for all IQR/Median<30%), as well as the manufacturer recommendation of confidence >60% for ElastQ to LSM results. Correlations of LSM by VCTE to LSM by ElastQ and ElastPQ were assessed by Pearson's correlation coefficient and concordance by Lin's correlation coefficient (CCC). Optimal Youden, specific rule-in and sensitive rule out-cutoffs for significant ≥F2 and F4 fibrosis were calculated.
Results: We included 175 consented patients. Median age was 60.5 [IQR:22] years, M:98 (53%), W:86 (47%), median BMI: 24.9 [5.7] kg/m2, and ALT: 28 [30] U/L. As defined by VCTE 90 (51.4%) had F0/F1 (≤8.3 kPa), 85 (48.6%) ≥F2 (>8.4 kPa) and 58 (33.1%) F4 (>12.8 kPa) fibrosis stage. Main etiologies were HCV: 101, HBV: 23, NAFLD: 20 and ALD: 22. We found a high correlation of ElastQ ($r = 0.54$, $p < 0.001$)) and ElastPQ ($r = 0.72$ ($p < 0.001$)) with VCTE (Fig-1a/b). The concordance was 0.23 (0.12–0.34) and 0.58 (0.38–0.73), respectively (Fig-1c/d).
The optimal ElastQ cutoff for ruling out ≥F2 fibrosis was at <7.1 kPa (Sens: 0.92, Spec: 0.84) and for ruling in ≥F2 at ≥8.1 kPa (Sens: 0.85, Spec: 0.92). ElastPQ cutoffs for ≥F2 were <6.35 kPa (Sens: 0.91, Spec: 0.85) for ruling-out and ≥7.1 kPa (Sens: 0.85, Spec: 0.91) for ruling-in ≥F2, respectively.

For F4 cirrhosis, optimal ElastQ cutoffs for ruling-out were at <8.1 kPa (Sens: 0.85, Spec: 0.75) and for ruling-in at >9.7 kPa (Sens: 0.74, Spec: 0.85). For ElastPQ, the cutoff for ruling-in and -out F4 cirrhosis were at <8.0 kPa (Sens: 0.85; Spec: 0.75) and >9.7 kPa (Sens: 0.74; Spec: 0.85), respectively.
Conclusion: LSM by the ElastQ (2D-SWE) and the ElastPQ (pSWE) technology accurately reflect liver fibrosis stages in patients with different etiologies of liver disease.

SAT244

Liver function assessment by 13C-methacetin test before and after placement of a transjugular portosystemic shunt: a prospective pilot study

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Background and Aims: Transjugular intrahepatic portosystemic shunt (TIPS) placement can lead to severe complications such as hepatic encephalopathy or acute-on-chronic liver failure. Risk factors for the development of such post-TIPS complications are ill-defined. A point-of-care diagnostic ^{13}C-methacetin test for the determination of maximal liver function capacity (LiMAx®) has been developed and validated by predicting adequately post-operative liver failure after liver resection (Stockmann M et al. J Hepatol 2012 & Annals of Surgery 2009). The aim of this prospective study is to evaluate the performance of LiMAx® before and after TIPS placement and to ideally correlate pre-TIPS measurements to post-TIPS outcomes.
Method: Patients undergoing TIPS for refractory ascites, secondary prevention of variceal bleeding and/or for partial portal vein thrombosis on imaging with the danger of complete thrombosis were included. Patients undergoing TIPS placement were tested before (−1 day) and after (+1, +7, +28, +72 and +180 days) the intervention for: LiMAx®, hepatic encephalopathy (HE; critical flicker frequency, Stroop & connect the numbers test), laboratory (MELD score) as well as imaging of the TIPS flow by Doppler ultrasound. Patients with TIPS indication for acute bleeding (<72 h), presence of HCC, CHILD >12, or overt HE or right heart failure were excluded.
Results: 15 patients (13 male/2 female, mean age 63 (48–71) years, range) with a mean CHILD 7.8 (5–9) and MELD 9.0 (6.4–14) were included (TIPS indications: ascites n = 9, varices n = 3, portal vein thrombosis n = 3). ^{13}C-methacetin test showed a rapid, persistent and significant decline after TIPS placement (day 0: 218 ug/kg/h (range 753–61) vs. day 7: 139 ug/kg/h (559–43), p = 0.0024). This drop was paralleled by worsening of liver function assessed by MELD score (day 0: 9.0 (6.4–14.0) vs. day 7: 11.5 (8.5–18.9), p = 0.0019). In contrast, HE testing did not correlate with decrease in of LiMAx®.
Conclusion: Our results indicate that the ^{13}C-methacetin (LiMAx) test is a sensitive method for capturing decrease in liver function after TIPS placement. LiMAx decrease is paralleled by increase in MELD score after TIPS placement. A larger study is needed to assess the value of LiMAx testing as predictor for post-TIPS complications.

SAT245

A novel diagnostic model using liver stiffness measurement and platelet count that accurately predicts the presence of portal hypertensive gastropathy in patients with cirrhosis

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Background and Aims: Portal hypertensive gastropathy (PHG) and esophageal varices (EV) are common complications of cirrhosis and portal hypertension that require endoscopic screening for diagnosis. The objective of the study is to predict the presence of PHG and EV using noninvasive markers of chronic liver disease.
Method: This was a cross-sectional, retrospective study in patient with chronic liver disease using clinical, biochemical, endoscopic, and histological data. Multivariate analyses were performed to identify the variables associated with the presence of PHG and EV. Receiver operator characteristic (ROC) curves were constructed for single variables and combinations of variables and compared to established models of liver fibrosis. Optimal cutoffs for sensitivity/negative predictive value and specificity/positive predictive value were derived from the curves.
Results: 151 patients were included in the study, of which 54.7% had cirrhosis confirmed by liver biopsy. Additionally, 29.7% had PHG and 32.5% had EV diagnosed by endoscopy. Univariate analysis showed PHG was associated with: older age (p = 0.006), increased transient elastography (TE) (p = <0.001), cirrhosis (p = 0.001), lower platelet count (p = <0.001), increased INR (p = <0.001), increased AST (p = 0.019), increased alkaline phosphatase (p = <0.001), elevated bilirubin (p = 0.007), and lower albumin (p = <0.001). Multivariate analysis showed that lower platelet count (p = 0.023) and increased TE (p = 0.015) were the only variables associated with the presence of PHG. Using the multivariate analysis, we developed a diagnostic model incorporating TE and platelet count: TE-PLT (TE divided by the platelet count). The area under the ROC (AUROC) for TE-PLT (AUROC = 0.867) was superior to TE alone (AUROC = 0.838), FIB4 (AUROC = 0.822), APRI (AUROC = 0.803), AAR (AUROC = 0.650), and AARPRI (AUROC = 0.795). In a range of cutoffs at 0.0675 to 0.1921 for TE-PLT, the lower value had NPV/sensitivity of 90% and upper value had PPV/specificity of 90%, indicating a good test sensitivity and specificity. Similarly, ROC curves for the presence of EV showed TE-PLT (AUROC = 0.805) to be superior to TE alone (AUROC = 0.782), FIB4 (AUROC = 0.723), APRI (AUROC = 0.703), AAR (AUROC = 0.573), and AARPRI (AUROC = 0.719). In a range of cutoffs at 0.0402 to 0.2041 for TE-PLT, the lower value had NPV/sensitivity of 90% and upper value had PPV/specificity of 90%. In conjunction to the AUROC curves, PHG had a higher correlation with cirrhosis (Spearman coefficient = 0.463, p = <0.001) than EV (Spearman coefficient = 0.435, p = <0.001), suggesting PHG to be a more sensitive indicator of portal hypertension in cirrhosis.

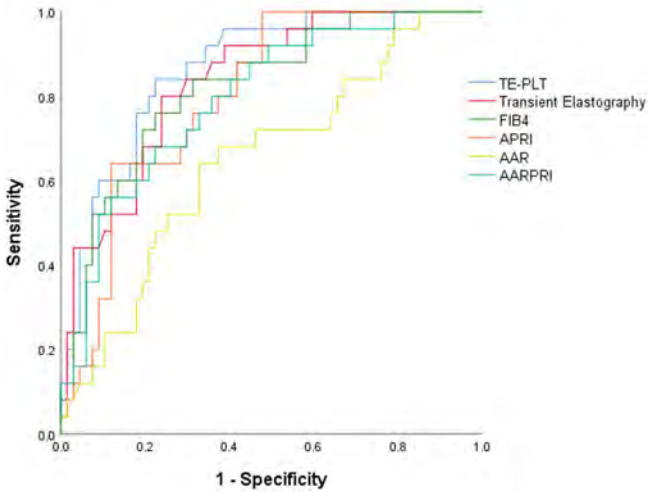

Figure: Area under the curve (AUROC) for TE-PLT compared to other non-invasive models of fibrosis in detecting the presence of PHG.

Conclusion: The novel TE-PLT index accurately predicts the presence of PHG and EV compared to other models of liver fibrosis.

SAT246

Endothelin-1 level at first presentation of hematemesis as indicator of recurrent bleeding within 5 days

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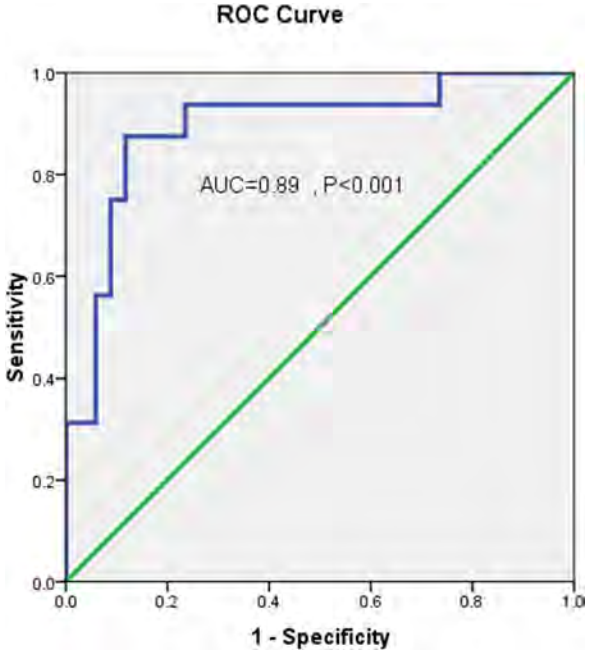
Background and Aims: Acute variceal bleeding is a severe complication of portal hypertension carrying an overall 6-week mortality of 10–30% according to degree of liver dysfunction. Previous studies demonstrated that peripheral and hepatic levels of endothelin-1 (ET-1) have been correlated with the stage of portal hypertension determined invasively by hepatic venous pressure gradient (HVPG) and degree of liver insufficiency in patients with liver cirrhosis. The aim of this study is to evaluate serum level of ET-1 as a non-invasive predictor of early variceal rebleeding within 5 days after endoscopic control.

Method: Out of 66 patients presented to our endoscopy unit between March 2019 and August 2019, written informed consents were obtained from 50 patients who had been enrolled in this prospective study, presented with proved esophageal acute variceal bleeding on endoscopy as a complication of Hepatitis C virus induced liver cirrhosis and portal hypertension. All patients were subjected to routine laboratory investigations and assessment of serum level of ET-1 prior to endoscopic therapy. Patients were grouped into 2 groups on basis of early rebleeding within 5 days after endoscopic control: group A included 16 patients who developed rebleeding within 5 days and group B included 34 patients with no recurrent bleeding in the same follow up period.



Results: Stepwise multivariate logistic regression analysis showed that 2 variables were independent risk factors for early rebleeding: ET-1 level [odds ratio (OR) 1.05, 95% CI: 1.02–1.08, $p < 0.001$] and serum albumin level (OR 0.006, 95% CI: 0.001–0.83, $p = 0.04$). At the best cut-off value of ET-1 level at 65.29, the specificity of prediction of 5 days variceal rebleeding was 88.2%, the sensitivity was 87.5%, accuracy was 88% and area under the curve (AUC) was 0.89. Furthermore, ET-1 level was significantly higher in patients presenting with more advanced portal hypertensive endoscopic findings particularly the number of variceal cords ($p = 0.006$) as well as post bleeding adverse events including drop in hemoglobin level ($p = 0.002$) and degree of renal impairment ($p < 0.001$). Interestingly, ET-1 level showed significant correlation with the duration of hospital stays ($p < 0.001$).

Conclusion: Serum ET-1 level appears to be effective, convenient and non-invasive predictor of not only early variceal rebleeding but also associated comorbidities such as degree of renal impairment and duration of hospital stay.

SAT247

Spleen acoustic radiation force impulse (ARFI) elastography predicts decompensation in patients with liver cirrhosis

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Background and Aims: Hepatic venous pressure gradient(HVPG) predicts prognosis in liver cirrhosis(LC). However, it is invasive and not available in most centers. Our aim was evaluate hepato-splenic ARFI elastography to predict prognosis in LC.

Method: Consecutive patients with LC and HVPG measurement were included prospectively and followed up until death, liver transplant or last day of follow-up. Exclusion criteria: hepatocellular carcinoma out Milan-Criteria, portal thrombosis and refuse to participate. On the same day of the HVPG measurement, laboratory test and abdominal ultrasound with hepato-splenic ARFI were performed. Data from transient hepato-splenic elastography were collected if was performed at least 6 month before.

Results: From November 2010 to November 2019, 76 patients were included.73.7% males, mean age 56(DE8). Main etiologies: HCV 43.4%,AFLD/NAFLD 42.1%. Mean MELD 10.4(DE3.8) and CHILD PUGH A/B/C 80.9%/11.8%/7.3%. 58(76.3%) were compensated. Mean follow-up 41 months (2–108). 10(13.2%) died and 5(6.6%) were transplanted during follow-up. Mean HVPG(mmHg) was 15.5(De5.7), mean ARFI hepato-splenic elastography(m/s) was 2.6(SD0.7) and 3.2(SD 0.5) respectively, hepato-splenic transient elastography (KPa) was 32.1(SD 17.6) and 66.3(SD11.8) respectively. HVPG showed a moderate correlation with splenic ARFI($r = 0.5$;$p = 0.001$) and hepatic Fibroscan®($r = 0.5$;$p < 0.001$).20 out of 58 compensated patients (34.5%) had first hepatic decompensation(HD) during follow-up. Factors related to HD were: albumin(g/dL) 3.7(SD0.6)vs4.0(SD0.4);$p = 0.03$, MELD 12.0 (SD2.9)vs8.8 (SD2); $p = 0.001$; HVPG 17.2(DE5.9) vs13.4 (DE5.1); $p = 0.01$, splenic ARFI(m/s)3.3(0.5); $p = 0.04$vs3.0 (DE0, 5) and spleen diameter(cm) 15.4(2.7)vs13.2(2.6); $p = 0.03$. In the multivariate analysis, MELD showed a HR 1.3(1.1–1.8); $p = 0.03$ and splenic ARFI a HR3.7(1.1–12.8); $p = 0.04$. The AUC of the ROC curve of splenic ARFI and MELD to predict HD was 0.8 and 0.8 respectively. A splenic ARFI cutoff≥3 m/s had high sensitivity 95% and high NPV 94%. The accumulated probability of HD at 12 and 24 months was: splenic ARFI ≥3 m/s: 29% and 43.8% and<3 m/s: 5.6% and 5.6%; $p = 0.001$. Factors related to death in the global cohort were: MELD 18.3(DE2.8) vs9.3(DE2.4);$p < 0.001$, albumin(g/dL)3.3(SD0.6) vs4.0(SD0.5), bilirubin(mg/dL)2.8(SD3.0) vs.1.4(SD1.4);$p = 0.02$ and spleen size(cm) 16(SD3.7)vs13.7(SD2.6); $p = 0.02$.

Conclusion: Splenic ARFI elastography and MELD predict HD in compensated patients with LC. Patients with splenic ARFI ≥3 m/s are at high risk of HD.

SAT248

Automatic high-risk fibrosis score prediction using computed tomography imaging

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Background and Aims: Hepatic fibrosis diagnosis is important for risk stratification, prognosis evaluation and monitoring of treatment response. We have previously shown that computer tomography (CT) perfusion imaging and splenic radiomics can accurately assess and grade liver fibrosis. Using this methodology, the objective of this study is to identify patients whose tumors are at high risk of recurrence after hepatic resection.
Method: Ninety-four patients with focal liver lesions referred for liver resection underwent a pre-surgery standard triphasic contrast CT scan. The patients also had excised tissue samples graded for fibrosis by histopathology per the METAVIR scoring system (F0-F4). A logistic regression algorithm was used to model the relation between hepatosplenic radiomics and fibrosis stages. The dataset was split between a training and a validation set according to fibrosis stages. A logistic regression algorithm was used to model the relation between hepatosplenic imaging features and advanced fibrosis stages. The subsequent high-risk Fibrosis score is then correlated to the recurrence event.
Results: Receiver operator curves show the performances in the training (AUC = 0.83) and validation dataset (AUC = 0.91). Clinical prediction performances were comparable in the training (Sensitivity = 75%, Specificity = 93%, NPV = 93%, PPV = 75%) in the validation (Sensitivity = 86%, Specificity = 100%, NPV = 82%, PPV = 100%) dataset. Kaplan-Meier survival analysis was used to correlate fibrosis risk with the clinical outcome defined as recurrence free survival (RFS). Cox-regression modelling of recurrence hazard ratios showed similar results for histology scores (HR = 6.6, pval < 0,01) and non-invasive fibrosis scores (HR = 4.1, pval < 0,01). When combining the histology (invasive) and non-invasive methods we are able to stratify the low risk recurrence group as defined by histology in two sub-groups with significant differences (pval < 0.05) in recurrence free survival outcome.
Conclusion: A fully automated hepatosplenic radiomics quantification is used as a non-invasive method to identify liver high-risk fibrosis score. Prognosis of patients that underwent liver tumor resection is accurately derived from the developed advanced fibrosis score. Further validation is warranted to determine high risk fibrosis prognostic value in independent cohorts.

SAT249

The variscreen algorithm using successively platelets, liver stiffness and INR improves and secures the screening of esophageal varices needing treatment

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Background and Aims: Based on platelets and liver stiffness measurement (LSM by vibration-controlled transient elastometry), the Baveno VI criteria (B6C), the expanded B6C (EB6C) or the ANTICIPATE score can be used to rule out varices needing treatment (VNT). We aimed to evaluate and improve these tests.

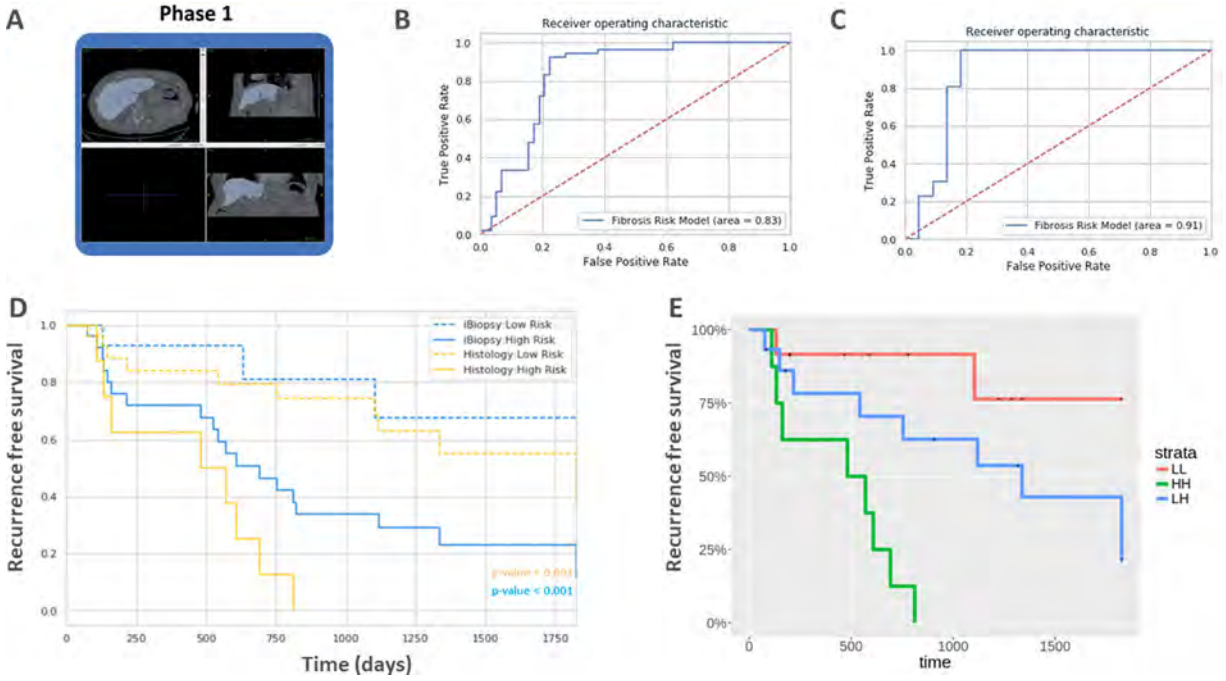
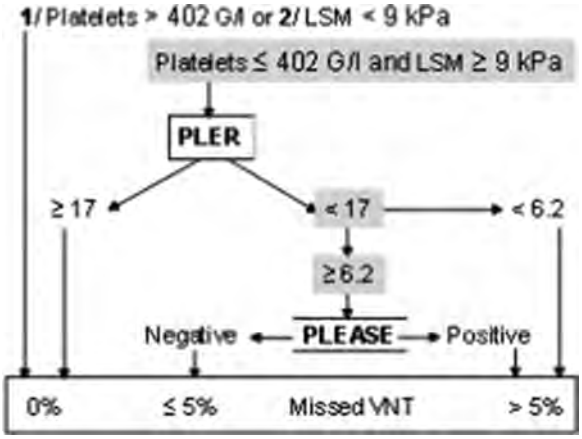


Figure: (abstract: SAT248): Fibrosis risk prediction. A) Hepatic fibrosis is analyzed both in the liver and its adjacent organs (spleen is used in this study). Receiver operator curves show the performances in the B) training and C) validation dataset. D) Kaplan-Meier survival analysis was used to correlate fibrosis risk with the clinical outcome defined as recurrence free survival (RFS). E) Stratification of histology low risk group into two sub-groups : Low-Histology & Low-iBiopsy (in red) and Low-Histology & High-iBiopsy (in blue).

Method: 2368 patients were randomized in derivation (2/3, n = 1579) and validation (1/3, n = 789) populations with chronic liver diseases (CLD) of various etiologies and severities in a multicenter retro-prospective study. Published tests were compared to two new tests: PLER (platelets/LSM ratio) and PLEASE (PLER adjusted on etiology/sex/INR). In the derivation population, patient characteristics were: VNT: 15.1%, etiologies: viral: 50.2%, NAFLD: 28.9%, alcoholic: 20.8%, MELD score: 9.5 ± 3.0, LSM≥10 kPa: 93.0%. Patient characteristics were not significantly different in the validation population.



Results: 1/Tests to diagnose VNT. AUROC for VNT were significantly different between scores: PLER: 0.761, ANTICIPATE: 0.770, PLEASE: 0.798. PLEASE score was better calibrated than other scores (Spearman's r: 0.37, $p < 0.001$). 2/Tests to spare endoscopy. Performances for spared endoscopy rate and safety for missed VNT rates (respectively, in parentheses) were, in increasing order: B6C: 23.9% (2.9%), ANTICIPATE: 24.3% (4.6%), PLER: 26.6% (4.6%), PLEASE: 34.8% (3.3%) and EB6C: 41.9% (10.9%). Differences in spared endoscopy rates were significant between tests ($p \leq 0.001$) except for B6C vs ANTICIPATE. Differences in missed VNT rates were significant only between EB6C vs other tests ($p \leq 0.009$). PLEASE was the only safe test (missed VNT ≤ 5%) whatever the sex or etiology. A VariScreen algorithm (Figure), based successively on platelets or LSM then PLER (in 94.2% of patients) then PLEASE (in only 35% of patients), secured screening with no missed VNT in poor liver function (MELD ≥ 10). The rates of VariScreen for spared endoscopy and missed VNT were 35.7% and 2.9%, respectively. Test performance and safety were not significantly different between populations. Tests and Variscreen algorithm can be calculated at http://forge.info.univ-angers.fr/~gh/wstat/pler-please-variscreen.php

Conclusion: B6C are safe for missed VNT rate regardless of CLD etiology and severity, and regardless of sex; EB6C are unsafe and no longer recommended. To improve current VNT screening, we propose the sequential VariScreen algorithm applicable to any main-etiology CLD and secured for liver severity.

SAT250

Breath-based monitoring of liver metabolism using exogenous volatile organic compounds - towards improved detection

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Background and Aims: Targeted analysis of the subset of metabolites exhaled as volatile organic compounds (VOCs) represents an attractive non-invasive means to measure the functional capacity of the liver. Limonene, an exogenous VOC (eVOC) we are regularly exposed to through diet and the environment, is metabolised by the CYP450 enzymatic complex. In this study, we tested the hypothesis that limonene reflects changes in liver function by analysing breath limonene levels of subjects with early-stage cirrhosis (Child-Pugh class (CP) A and B) and hepatocellular carcinoma (HCC).

Method: We collected breath samples from 26 healthy controls (65 [41–81] year, f/m [15/11]), 20 patients with cirrhosis (55 [35–78] year, f/m [9/11]), and 14 patients with HCC (69.5 [48–84] year, f/m [4/10]) using the ReCIVA Breath Sampler combined with a CASPER Portable Air Supply to reduce ambient contamination. Breath samples were analysed by thermal desorption gas chromatography mass spectrometry (TD-GC-MS), using a Q-Exactive GC hybrid quadrupole

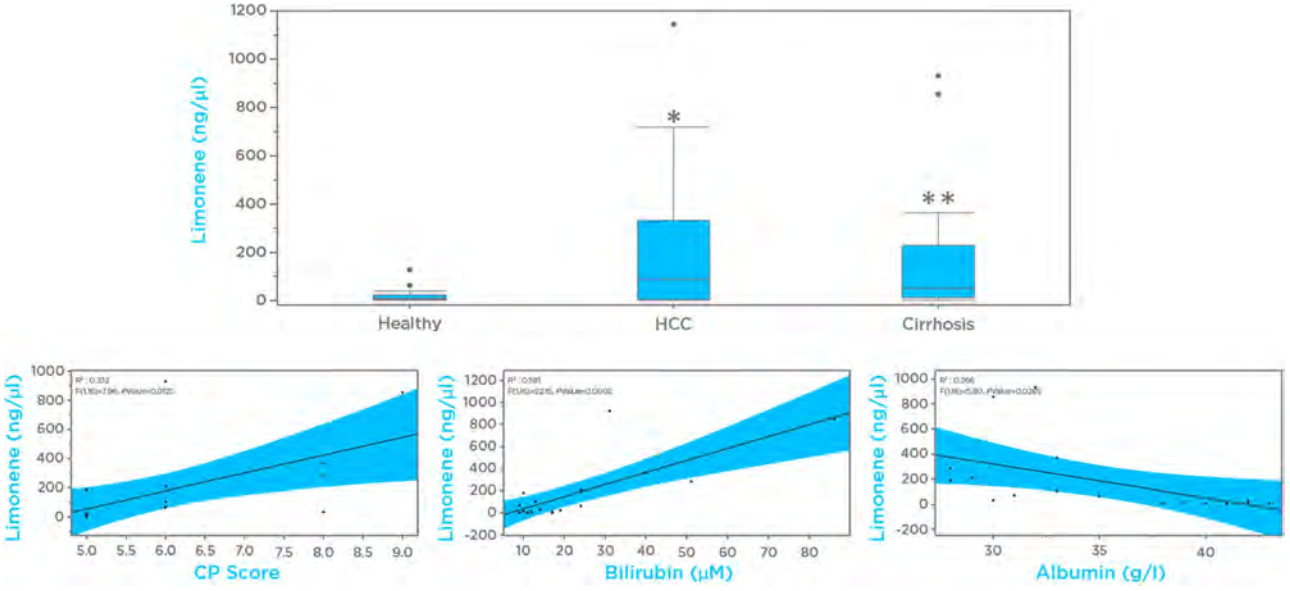

Figure: (abstract: SAT250)

Orbitrap mass spectrometer. Peak integration was performed with Chromeleon data system. Limonene standards were run to provide absolute quantitation. Limonene levels were compared groupwise by using a Mann-Whitney U-test.

Results: Limonene breath levels were significantly elevated in subjects with HCC (84.5, [0–1142] ng/µl) and cirrhosis (47.9 [0.3–928] ng/µl) compared to controls (5.9, [0–124] ng/µl), (p-value 0.03 and 0.004, respectively). A subset of subjects with HCC and cirrhosis showed near normal levels of exhaled limonene. A bivariate linear regression inference revealed that breath limonene correlates with the Child-Pugh (CP) score ($p = 0.01$, $R^2 = 0.3$), and serum bilirubin levels in patients with cirrhosis ($p = 0.0002$, $R^2 = 0.6$), but not in patients with HCC ($p = 0.53$, $R^2 = 0.04$; $p = 0.73$, $R^2 = 0.0.011$). Similarly, a negative correlation with albumin levels was found in subjects with cirrhosis ($p = 0.02$, $R^2 = 0.3$).

Conclusion: Exhaled limonene levels are significantly elevated in subjects with cirrhosis and/or HCC and reflect cirrhosis severity, detoxifying capacity, and protein synthesis, as demonstrated by correlations with CP score, bilirubin, and albumin serum levels. The observed spread of limonene levels could be related to differences in enzymatic activity, disease severity and/or limonene exposure. These data demonstrate that analysis of breath VOCs can probe specific hepatic pathways for the extraction of clinically relevant information related to liver function.

SAT251

Intelligent liver function testing in action: a one-year review

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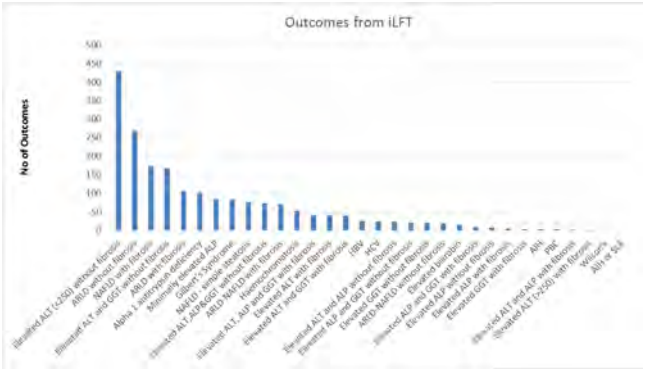
Background and Aims: Liver Function Tests (LFTs) are abnormal in 20% of cases in primary care, and mortality from chronic liver disease continues to rise. Intelligent liver function testing (iLFT) was launched in the Tayside region of Scotland in August 2018. General Practitioners (GPs) provide data on alcohol intake, BMI and comorbidities, and those with abnormal LFTs have reflex tests without further venepuncture. GPs are then provided with management plans with a recommended outcome: secondary care referral for fibrosis assessment or complex treatment; primary care follow-up of early or simple liver disease; or when a diagnosis is unclear, staging information and referral criteria. iLFT is designed to improve diagnosis of liver disease and as a result, improve the quality of further investigations while optimising the time of referral to secondary care. This will reduce both mortality and cost to practitioners.

Method: A retrospective analysis was performed of all patients who had iLFT requested in the first year (August 2018 – August 2019) of the live system, recording the outcome(s) for each request.

Results: 2362 iLFT requests were received in the one year from launch. 160 (6.8%) were rejected. 378 (16%) had normal LFTs and thus iLFT did not cascade. There were 1824 (77.2%) requests with at least one abnormal liver enzyme, resulting in iLFT cascade and 2013 diagnostic outcomes. The most common outcome was isolated ALT elevation without fibrosis (23.5%), followed by alcohol related liver disease without fibrosis (14.7%) and non-alcoholic fatty liver disease with fibrosis (9.4%). The frequency of each outcome is shown in Figure 1. iLFT recommended patients be referred to secondary care in 509 (25.3%) outcomes (of which 393 (77.2%) were for further assessment of fibrosis only), with 1504 (74.7%) recommending primary care management.

Conclusion: iLFT safely and rapidly detects patients at risk of chronic liver disease using reflex fibrosis scores and autoimmune, virology and genetic tests. Only 25% of patients with abnormal LFTs had secondary care referral recommended, allowing 75% to be managed in primary care. GPs are currently using iLFT to investigate patients known to have abnormal LFTs, rather than a screening tool, so the number requiring referral should fall once this pool has been exhausted. iLFT is improving the diagnosis of liver disease and ensuring patients who require secondary care are seen, whilst reducing unnecessary referrals.



SAT252

ALT level in the diagnosis of chronic liver disease and advanced fibrosis

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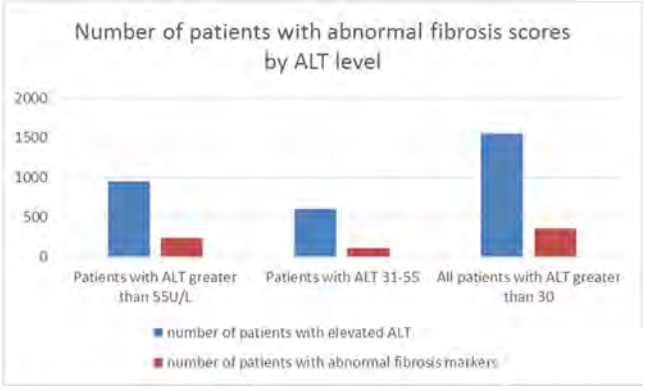
Background and Aims: Serum level of alanine aminotransferase (ALT) is one of the most common parameters used in the assessment of liver disease. Mortality from chronic liver disease is continuing to rise, in part due to late diagnosis or recognition of signs and symptoms. Historically, our laboratory has used an upper limit of normal (ULN) of 55 U/L for ALT. However, there is significant evidence suggesting an ULN of 30 U/L or even lower should be used, dependent on sex. Intelligent Liver Function Testing (iLFT) is an automated algorithm which aims to use co-morbidities and alcohol intake to diagnose liver disease earlier and streamline patient management between primary and secondary care. We aimed to assess how many extra patients were diagnosed with abnormal fibrosis markers if an ALT ULN of 30 U/L was used rather than 55 U/L in our population.



Method: A retrospective analysis of all patients who had iLFT performed between August 2018 and 2019 was performed. Each

patient had non-invasive fibrosis markers performed (NAFLD score and FIB4 score) and the result of the iLFT algorithm for each patient was noted. This was then assessed in conjunction with their ALT.
Results: 948 patients had an ALT greater than 55U/L. Of these patients, iLFT recommended 317 (33.4%) be referred to secondary care; 243 (25.6%) of whom had abnormal fibrosis scores and required assessment for liver fibrosis. However, a further 601 patients had an ALT greater than 30 U/L but less than 55 U/L, resulting in a total of 1549 patients. iLFT recommended 148 (24.6%) patients with ALT 31–55 be referred to secondary care; 114 (18.9%) had abnormal fibrosis scores requiring further assessment, as shown in Figure 1.
Conclusion: Lowering the ULN of ALT from 55 to 30 in our population identified an additional 114 patients with abnormal fibrosis scores, increasing the detection of patients requiring further assessment for fibrosis in secondary care from 15.7% to 23.0% of all patients with ALT >30 U/L. This provides the potential to diagnose chronic liver disease in more patients, allowing the timely recommendation of lifestyle intervention and therapeutics.

SAT253

Multiparametric magnetic resonance imaging of liver and spleen is a reliable non-invasive predictor of clinically relevant hepatic venous pressure gradient thresholds and predicts failure of primary prophylaxis for variceal bleeding

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Background and Aims: Multiparametric MRI (mpMRI) of the liver and spleen is a promising modality for non-invasive assessment of portal hypertension, offering a potential alternative to hepatic venous pressure gradient (HVPG) measurement, which is invasive and not widely available. Clinically relevant HVPG thresholds include (i) HVPG ≥ 10 mmHg, which defines clinically significant portal hypertension (CSPH) and predicts decompensation, (ii) HVPG > 12 mmHg, which predicts increased risk of variceal bleeding, and (iii) HVPG > 16 mmHg, which is associated with increased mortality. This study aims to evaluate the reliability of mpMRI of liver and spleen to predict clinically relevant HVPG thresholds (HVPG ≥ 10 mmHg, HVPG > 12 mmHg, HVPG > 16 mmHg) and development of variceal bleeding in a cohort of patients with chronic liver disease.
Method: Patients scheduled to undergo HVPG measurement for evaluation of portal hypertension were prospectively recruited for this IRB-approved study. All subjects underwent paired HVPG measurement and mpMRI (Liver*MultiScan*™, Perspectum Diagnostics, UK) to measure liver cT1 (assesses liver fibrosis and inflammation, corrected for iron) and spleen cT1 (assesses splenic congestion). Correlation between HVPG and mpMRI parameters (liver cT1 and spleen cT1) was evaluated using Pearson co-efficient and their performance for prediction of the various HVPG thresholds and variceal bleeding was evaluated using AUROC statistics.
Results: Forty subjects were enrolled, 50% males with median age of 64 years. Liver cirrhosis was present in 37 subjects (57% Child A). Median HVPG was 14 mmHg (IQR 12–17). 37 subjects had HVPG ≥ 10 mmHg (92.5%), 26 had HVPG > 12 mmHg (60%) and 12 had HVPG > 16 mmHg (30%). There was a weak but significant correlation between HVPG and liver cT1 (r = 0.316, p = 0.05) but not with spleen cT1. Liver cT1 was a good predictor for CSPH (AUROC 0.815, 95%CI 0.638–0.991) and a moderate predictor for HVPG > 12 mmHg (AUROC 0.737, 95%CI 0.564–0.911) and HVPG > 16 mmHg (AUROC 0.728, 95% CI 0.567–0.889). Spleen cT1 was not a reliable predictor for any of the pre-determined HVPG thresholds. However, spleen cT1 was found to be an excellent predictor of variceal bleeding, particularly in the subgroup of patients on beta-blocker treatment (AUROC 0.950, 95%CI 0.854–1.000) with 100% sensitivity, 87% specificity, 67% PPV and 100% NPV at a cut-off value of 1395 ms.
Conclusion: Multiparametric MRI is a potential non-invasive biomarker for assessment of portal hypertension. Liver cT1 is a reliable predictor for clinically relevant HVPG thresholds of HVPG ≥ 10, HVPG > 12 and HVPG > 16 mmHg. Spleen cT1 is an excellent predictor of patients at risk of failure of primary prophylaxis for variceal bleeding.

SAT254

Serum keratin 19 (CYFRA 21-1) links ductal reaction with portal hypertension and outcome of advanced liver disease

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Background and Aims: Keratins (Ks) represent tissue-specific proteins. K18 is produced in hepatocytes while K19 – the most widely used ductal reaction (DR) marker – is expressed in cholangiocytes and hepatic progenitor cells. K18-based serum fragments are commonly used liver disease predictors, while K19 fragments detected through CYFRA 21-1 are established tumor but not liver disease markers yet. Since DR reflects the severity of underlying liver disease, we evaluated the relevance of CYFRA 21-1 in patients with different liver disease severities and etiologies.
Method: Hepatic expression of ductular keratins (K7/K19/K23) was analyzed in 57 patients with chronic liver disease (cohort i). Serum CYFRA 21-1 levels were measured in 52 German alcohol misusers undergoing detoxification (cohort ii), 333 Austrian patients with advanced chronic liver disease (ACLD) of various etiologies undergoing hepatic venous pressure gradient (HVPG) measurement (cohort iii), 231 French patients with compensated alcoholic cirrhosis (median follow-up 73 months; cohort iv), and 280 German patients with decompensated cirrhosis of various etiologies (cohort v).
Results: Hepatic K19 levels were comparable among patients with F0-F3 fibrosis stages, but significantly increased in patients with cirrhosis (i). Hepatic K19 mRNA strongly correlated with expression levels of other DR-specific keratins. Among alcohol misusers (ii), similar CYFRA 21-1 serum levels were seen in individuals before and after detoxification therapy indicating that CYFRA 21-1 is a rather stable parameter. CYFRA 21-1 levels were increased in patients with higher vs. lower liver stiffness (LSM ≥ 15 kPa; 3.71 vs. 1.42 ng/mL, P = .002). In line with that, CYFRA 21-1 levels were strongly associated with the presence of clinically significant portal hypertension (CSPH; HVPG ≥ 10 mmHg) (OR = 5.87 [2.95–11.68]) and mortality (HR = 3.02 [1.78–5.13]) in patients with ACLD (iii). In patients with compensated cirrhosis (iv), elevated CYFRA 21-1 levels indicated increased long-term risk of death/liver transplantation (HR = 2.59 [1.64–4.09]). In hospitalized patients with decompensated cirrhosis (v), CYFRA 21-1 levels predicted 90-day mortality (HR = 2.97 [1.92–4.60]) and its diagnostic accuracy (AUROC 0.64) was

comparable to the composite scores MELD (0.70) and ACLF grade (0.68).
Conclusion: Hepatic K19 mRNA and serum CYFRA 21-1 levels rise in cirrhosis, are strongly associated with the presence of CSPH and reliably predict mortality. The widely available serum CYFRA 21-1 constitutes a novel, DR-related biomarker with prognostic implications in patients with different settings of liver disease.

SAT255

Relationship between Laennec histological subclassification of cirrhosis and clinical stage, grade of portal hypertension and liver stiffness

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Background and Aims: Currently used histological staging systems group all patients with cirrhosis into a single category, without taking account severity of cirrhosis. Subclassification of cirrhosis using the Laennec staging system has been proposed but has been mainly evaluated in patients with hepatitis B in Asia. In the present study, we assessed, in a well-characterized cohort of Western patients, relationship between Laennec subclassification of cirrhosis and clinical severity, grade of portal hypertension and liver stiffness.
Method: Ninety patients with cirrhosis (median age 59 yrs; Male 66%; etOH 42%, viral 27%, NASH 27%), who underwent hepatic venous pressure gradient (HVPG) measurement and liver stiffness measurement (LSM), using transient elastography (TE), as part of work-up before liver transplant or liver resection were included. Cirrhosis was subclassified on either liver biopsies or explanted/resected livers by a single pathologist (VP) blinded to clinical data, using the Laennec scoring system, into three groups (4a: thin septa; 4b: at least two broad septa and 4c: at least one very broad septum or many minute nodules).
Results: Stages of cirrhosis were distributed as follows: 4a: 38%, 4b: 47% and 4c: 16%. Results are detailed in the figure. As compared with 4a, patients with 4b/4c were more severe clinically (higher Child Pugh and MELD scores), had more severe portal hypertension (higher proportion of patients with HVPG ≥10 mm Hg, increased frequency of variceal bleeding and ascites) and higher LSM values. LSM values significantly increased with Laennec stages (4a: 17 (10–27) kPa; 4b: 38 (27–51) kPa; 4c: 68 (48–75) kPa; $p < 0.001$)

Table: Relationship between Laennec stages, clinical severity, HVPG and LSM

Variables	Laennec 4a n = 34	Laennec 4b n = 42	Laennec 4c n = 14	4a vs 4b/4c *p*
Clinical severity				
Child A/B/C (%)	85/12/3	48/43/9	14/21/64	<0.001
MELD score	9 (7–11)	10 (8–14)	18 (12–23)	0.01
Hemodynamic data				
HVPG (mm Hg)	10 (6–11)	18 (12–21)	18 (14–23)	<0.001
HVPG ≥ 10 mm Hg (%)	53	86	100	<0.001
LSM (kPa)	17 (10–27)	37 (27–51)	68 (48–75)	<0.001

Conclusion: Laennec subclassification of cirrhosis correlates well with clinical stage of cirrhosis and severity of portal hypertension. Liver stiffness, using transient elastography, seems to be a good surrogate of these different cirrhosis stages.

SAT256

Evolving imaging in biliary disease: quantitative magnetic resonance cholangiopancreatography findings correlate with the modified Amsterdam score in patients with primary sclerosing cholangitis

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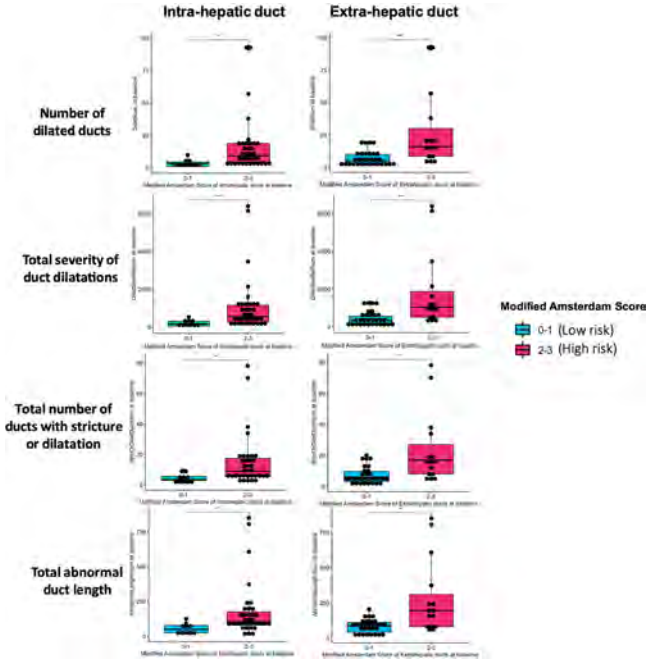
Background and Aims: Quantitative magnetic resonance cholangiopancreatography (MRCP+) is a novel non-invasive imaging technique for quantifying biliary tree volume, duct diameters, and dilated/strictured regions in hepatobiliary disease. It is designed to address the limitations of traditional MRCP interpretation which can have large inter-observer variations. The aim of this study is to investigate the utility of quantitative MRCP in a prospective study of patients with primary sclerosing cholangitis (PSC) and evaluate its correlation with the modified Amsterdam cholangiography score.
Method: In this study, patients with established PSC (n = 45) were recruited and scanned on a Siemens Verio 3 T system with standardised MRCP imaging. The tubular structures of the biliary system were enhanced and quantified by MRCP+ using multi-scale Hessian analysis, gradient vector flow analysis, an intelligent path search algorithm and novel duct modelling algorithms. Each MRCP image was assessed by an experienced radiologist and evaluated using the modified Amsterdam score (mAms, intra-hepatic and extra-hepatic) to assess progression risk and categorized as low risk (0/1) or high risk (2/3).



Results: Assessment of intra-hepatic disease level measured by mAms revealed 10 PSC patients as low-risk and 35 as high-risk. High risk intra-hepatic patients were found to have a significant increase in the number of dilated ducts, the total severity of duct

dilatations, total number of ducts with strictures/dilatations, and total length in abnormal ducts compared to low-risk PSC patients (16.7 vs. 3.7, $p < 0.01$; 1083% vs. 205%, $p < 0.01$, 15.1 vs. 4.5, $p < 0.01$; 175 vs. 55 mm, $p < 0.01$, respectively). For extra-hepatic disease, 30 PSC patients were identified as low-risk, while 15 were assigned to the high-risk group. High-risk extra-hepatic PSC patients had a significantly higher number of dilated ducts (28vs. 7, $p < 0.001$), the total severity of duct dilatations (1791% vs. 437%, $p < 0.001$), total duct number with stricture/dilatation (23 vs.7, $p < 0.01$), and total abnormal duct length (278 vs. 82 mm, $p < 0.01$) when compared to low-risk PSC patients.

Conclusion: Quantitative MRCP reveals significant correlations with both intra-hepatic and extra-hepatic abnormalities as assessed by the modified Amsterdam score in PSC patients by an expert radiologist. Our findings support the ability of quantitative MRCP metrics to contribute to an objective stratification of biliary disease.

SAT257

The tissue balance of liver fibrosis: identification of fibrosis resolution biomarkers and demonstration of increased tissue formation and degradation

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Background and Aims: Fibrosis is described as accumulation of extracellular matrix (ECM) proteins and has long been considered a slow turnover disease with more tissue formation than degradation. A direct quantification of the tissue turnover balance, i.e. the ratio between formation and degradation, has been hampered consequent to the lack of available technologies.

The dense liver ECM, the fibrotic bands, consists of interstitial matrix (IM) produced by fibroblasts. Novel biomarkers reflecting tissue formation (fibrogenesis) and degradation (fibrolysis) separately may be able to quantify the velocity of tissue turnover including type I or III collagen formation (PRO-C1 or PRO-C3) as well as MMP-9 mediated degradation of type I and III collagen, C1M and C3M respectively.

We aimed to quantifying the relative amount of tissue balance by assessment of fibrogenesis and fibrolysis assays in vitro and in serum.

Method: Human primary fibroblasts were cultured in the scar-in-a-jar system. Soluble fibrogenesis and fibrosis resolution biomarkers were measured in the conditioned medium. After culture, the ECM of the fibroblasts were digested with MMP-9 to quantify fibrinolysis products, C3M and C1M. In addition, PRO-C3 and C3M were assessed in serum from 302 asymptomatic alcoholic liver disease (ALD) patients with biopsy confirmed Kleiner Fibrosis stage F0-F4 recruited in the EU H2020 GALAXY study.

Results: TGF-β induced collagen type III formation by 800% ($p < 0.0001$) and type I collagen formation by 250% ($p < 0.001$) quantified by PRO-C3 and PRO-C1, respectively. C1M and C3M were undetectable in the conditioned medium. After MMP digestion, C1M and C3M were 100 times ($p < 0.001$) higher as compared to undigested ECM. The ECM digest of TGF-β treated fibroblasts had 10 times increased levels of C1M and C3M as compared to vehicle control.

ALD patients with advanced fibrosis (F3-F4) showed an imbalance favoring fibrogenesis over fibrolysis with PRO-C3 elevated by 228% ($p < 0.0001$) for F0-2 vs. F3-4 whereas C3M was elevated 51% ($p < 0.0001$).

Conclusion: TGF-β clearly induced fibrogenesis biomarkers PRO-C3 and PRO-C1. In contrast, fibrolysis biomarkers were not detectable. After MMP-9 digestion, fibrolysis biomarkers were highly elevated suggesting that these biomarkers may be approximated of cell mediated tissue degradation. Interestingly, patients had 4X higher collagen formation than degradation in fibrosis, although both fibrogenesis and fibrinolysis were elevated.

SAT258

Systemic light chain AL with cardiac and liver involvement can be predicted by transient elastography

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Background and Aims: Transient elastography is the first elastography technique developed to quantitatively and noninvasively assess soft biological tissue stiffness. Liver stiffness (LS) is not specific to liver fibrosis and can be influenced by many factors, including amyloid deposits. The aim of our study was to examine whether amyloid deposition in the liver or other organs modifies LS and if there is any correlation with the liver functional tests.

Method: LS was measured prospectively in 72 patients with systemic light-chain amyloidosis (AL) that were investigated in the Hematology Department from Fundeni Clinical Institute. The diagnostic accuracy and cut-off values of LS for amyloidosis and its sensitivity and specificity were calculated.

Results: There was a significantly strong positive correlation between LS values and GGT ($r = 0.62$, $p < 0.0001$) or alkaline phosphatase values ($r = 0.49$, $p = 0.0001$), but a moderate positive correlation with serum total bilirubin ($r = 0.36$, $p = 0.003$) and AST values ($r = 0.26$, $p = 0.04$). There were significantly higher mean LS values in patients with hepatic AL involvement (37.4 ± 4.4 kPa vs 7.1 ± 0.9 kPa, $p < 0.0001$) patients with cardiac AL (25.2 ± 3.9 kPa vs 13.6 ± 3.5 kPa, $p < 0.0001$) and patients with splenic AL (30.8 ± 6.0 kPa vs 17.7 ± 3.1 kPa, $p < 0.0001$), but not in patients with renal AL. A cut-off value of 9.7 kPa, with an AUROC of 0.94, sensitivity and specificity >90%, is proposed for routine screening and diagnosis of significant AL liver infiltration. A cut-off value of 10.8 kPa, with an AUROC of 0.81 and a 100% sensitivity can be used to screen patients for multiple AL involvement (liver, cardiac and spleen).

Conclusion: LS > 9.7 kPa is suggestive of AL hepatic disease in patients with non-fibrotic liver changes, while higher levels (>10.8 kPa) are suggestive of multiple organs AL deposits.

SAT259

Validating the Swansea criteria in a single-centre study with cohorts of patients with acute fatty liver of pregnancy and haemolysis, elevated liver enzymes and low platelets syndrome: is it time to modify the criteria?

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Background and Aims: In clinical practice, it is very difficult to differentiate between acute fatty liver fatty of pregnancy (AFLP) and severe haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome. Although this does not impact on immediate

management, it is important to make the right diagnosis to aid long-term management, counselling and monitoring of future pregnancies. This study aims to ascertain the diagnostic value of the Swansea criteria in a cohort of patients with HELLP, as well as a group of women with AFLP.
Method: 30 patients with HELLP and 29 patients with AFLP were identified between 2000 and 2019 in our single centre study. Patients were identified as having AFLP based on clinical expertise, fulfillment of the Swansea criteria and liver biopsy where possible. The HELLP patients were identified through an Obstetrics database and were defined as having new onset hypertension during pregnancy with elevated liver enzymes and a platelet count of <150. Retrospective analysis of the patient demographics, biochemistry and clinical notes took place. Differences between the groups were analyzed with Fisher's Exact test.
Results: All the 29 patients with AFLP fulfilled the Swansea criteria with a score >/ = 6 (mean 8.1, range 6–11). Within the HELLP cohort, 11/30 patients (37%) fulfilled the Swansea criteria (mean 4.5, range 2–8). The Swansea criteria had a sensitivity of 100% in our cohort, with a specificity of only 63%. Polydipsia/polyuria (p = 0.0001), hypoglycaemias (p = <0.0001) and bilirubin to AST ratio >0.5 (p = 0.0002) were significantly more common in the AFLP group compared to the HELLP group. There were no significant differences in leucocytosis, urate levels and renal impairment between the groups. The liver enzymes post-delivery recovered quicker in the HELLP group compared to the AFLP group.
Conclusion: The Swansea criteria needs to be modified to allow better distinction between HELLP and AFLP in a clinical setting.

SAT260
Diagnostic performance of a new algorithm combining simple, non-invasive and inexpensive tests for predicting the presence of liver severe fibrosis and cirrhosis in patients with chronic hepatitis B
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Background and Aims: Various non-invasive methods for scoring fibrosis have been developed to overcome the limitations of liver biopsy. These technics have been not fully validated for the assessment of liver fibrosis in chronic hepatitis B. The objective of this study was to evaluate the usefulness of combining simple, non-invasive and inexpensive tests in terms of predicting liver severe fibrosis and cirrhosis in patients with chronic hepatitis B.
Method: This is a prospective cross-sectional study conducted on 408 consecutive patients from 3 centers who benefited from a liver biopsy for chronic hepatitis B. Using our cohort, we derived a decision tree, with a cost matrix penalizing type II error, predicting patients in stages F0-F1, F2 or F3-F4. The final decision contains nine leafs using the following variables: prothrombin time, platelets, ALT, GGT and age. We subsequently validated the decision three in an external cohort (n = 194).
Results: 408 patients in training set were used to create a "decision tree algorithm." In the validation cohort (n = 194), our "decision three algorithm" classified patients in F0-F1, F2 or F3-F4. Considering F0-F1 and F2 as negative test result, specificity was 94% for F0F1 and 67% for F2 patients respectively. Only 3 (1.5%) F3-F4 patient were classified as F0-F1. Negative predictive value was 96% and 89% for F0-F1 and F2 respectively.
Conclusion: A new algorithm combining simple, non-invasive and inexpensive test has a better diagnostic value than usual scores in predicting fibrosis in patients with chronic hepatitis B.

SAT261
Heat shock protein 47 is associated with fibrogenesis in alcoholic liver disease
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Background and Aims: Heat shock protein (HSP)47 is a collagen-specific intracellular chaperone essential for the formation of fibrillar collagens, known to be involved in pro-fibrotic wound-healing processes in comparison to the structural, laminar collagens. We hypothesized that a fragment of HSP47 is measurable in serum, related to biopsy-verified liver fibrosis reflected by histological assessment and associated with the type III collagen synthesis marker PRO-C3. For serological HSP47 assessment we developed a novel competitive enzyme-linked immunosorbent assay (ELISA).
Method: We included serum samples from a biopsy-controlled cross-sectional study of 301 alcoholic liver disease (ALD) patients and 50 gender, age and BMI matched healthy controls. Biopsies were scored according to Kleiner fibrosis stage (F0-4). A competitive ELISA employing a monoclonal antibody targeting the C-terminus of HSP47 (HSP47-C) was developed and technical validation was performed. PRO-C3 was evaluated for comparison. Mann Whitney and Kruskal Wallis tests were applied for intergroup comparisons in addition to Receiver operating characteristics (ROC) analysis and Spearman Rank correlation test. This study was conducted on behalf of the EU H2020 GALAXY consortium.
Results: The HSP47-C assay was technically robust and specific for the target sequence. Linearity was within the accepted range ± 20%. HSP47-C was elevated by 43% in ALD patients (mean 19.9 ng/ml, SD 13.3, p = 0.008) compared to healthy controls (mean 13.9, SD 6.8). In addition, HSP47-C was 73% higher for patients with F3–4 compared to F0-2 (p < 0.0001) with an AUC of 0.73 (p < 0.0001). In comparison PRO-C3 was elevated by 228% for F3-4 vs. F0-2 (p < 0.0001) with an AUC of 0.88 (p < 0.0001). HSP47-C was associated with PRO-C3 (rho = 0.26, p < 0.0001). When HSP47 and PRO-C3 were combined patients with F3-4 were 393% higher compared to F0-2 and with an AUC of 0.81.
Conclusion: The elucidation of collagen machinery may identify fibrosis drug targets and aid in segmenting liver fibrosis patients at the molecular level. The serological level of HSP47-C was higher in ALD as compared to healthy individuals and associated with the fibrogenesis markers PRO-C3 and Kleiner fibrosis stage. This suggests that HSP47 may be a potential target for anti-fibrotic therapy as well as being a marker for liver fibrosis.

SAT262
Dysregulation of wound healing status and activity is associated with fibrosis and inflammation in early alcohol associated liver disease
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Background and Aims: Wound healing is often discussed as being altered in fibrosis, but only assessed by standard biomarkers such as platelets and Von Willebrand factor (vWF). More advanced biomarkers of wound healing may provide additional knowledge. The aim of this study was to gain insights of the dynamics of fibrin/fibrinogen and vWF in patients with compensated alcoholic liver disease (ALD). PRO-Fib was selected to assess the conversion of fibrinogen to fibrin, as it measures the concentration of the pro-peptide when it is cleaved

of during the process. X-Fib was selected as a marker for fibrinolysis as it targets a fragment released from dissolved clots. vWF formation and degradation were evaluated by the N-terminal vWF propeptide (VWF-N) and a vWF fragment generated by ADAM-TS13 (VWF-A), respectively.
Method: Blood samples from 301 ALD patients were prospectively recruited and the ELISA based markers were evaluated: PRO-Fib, Fib-X, VWF-N and VWF-A. Histological assessment of inflammation (lobular and balloning, stage 0–5) and Kleiner fibrosis stage F0-4 were evaluated in liver biopsies from patients with a transient elastography >6 kPa, but without known cirrhosis. Associations between the biomarkers and histological findings were assessed by Kruskal-Wallis multiple comparison test. This study was conducted on behalf of the EU H2020 GALAXY consortium.
Results: FPA was significantly decreased according to fibrosis stages ($p < 0.0001$) and inflammation stage ($p < 0.0001$). In contrast, FPA in plasma, reflecting the active conversion of fibrin/fibrinogen was unaffected by fibrosis and inflammation. D-dimer was elevated in patients with inflammation ≥3 ($p < 0.02$) including portal inflammation ≥1 ($p < 0.0001$) or a fibrosis stage ≥2 ($p < 0.01$) compared to those without inflammation or fibrosis respectively. VWF-N was significantly higher in fibrosis stage F4 compared to F0-2 ($p < 0.04$). Also, VWF-A was significantly higher in F4 compared to F2 ($p = 0.005$). None of the vWF markers were associated with inflammation.
Conclusion: The dynamics of fibrin/fibrinogen and vWF are associated with pathological processes in progressive ALD. We found that the status of fibrin turnover was unbalanced with lower concentration of the fibrinogen/fibrin formation marker (FPA) evaluated in patients with presence of fibrosis or inflammation. High fibrinogen degradation activity (D-dimer) was associated with high fibrosis and inflammation scores. By contrast, both vWF formation (VWF-N) and degradation (VWF-A) were associated with increasing fibrosis stage. All together the presented data point towards an impaired wound healing response and quality in patients with fibrosis and compensated ALD.

SAT263
Liver stiffness measurement using acoustic radiation force impulse elastography is a good predictor of hepatic decompensation in pregnant cirrhotic patients
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Background and Aims: During pregnancy, elevated liver stiffness (LS) measured by transient elastography has been identified as a novel non-invasive screening parameter to predict women at risk for pregnancy-related complications such as preeclampsia. However, feasibility and safety of LS measurement (LSM) has not been studied using acoustic radiation force impulse elastography (ARFI). In addition, it's utility to predict hepatic decompensation post-delivery in pregnant cirrhotic patients is still unexplored.
Method: We prospectively recruited 224 pregnant women at the clinic of liver disease with pregnancy, Department of Endemic Medicine and Hepatology and Obstetrics and Gynaecology Department, Cairo University Hospital. LS was measured using ARFI elastography by Siemens ACUSON S3000 ultrasound system. LS was measured during the second trimester and 8–12 weeks post-delivery. Outcome of pregnancy (normal vs. complicated e.g. abortion, preterm labor, still birth & maternal mortality) and incidence of hepatic decompensation were assessed. All clinical and laboratory data were collected from patients records.
Results: In 224 pregnant women, we were able to measure LS with ARFI in 81% of the recruited subjects. Our cohort comprised 128 normal pregnancies, 37 patients with pregnancy related liver disease (Intrahepatic cholestasis (n = 6), preeclampsia (n = 23), and hyperemesis gravidarum (n = 8)) and 59 patients with established chronic liver disease not related to pregnancy (chronic viral hepatitis B and C and autoimmune hepatitis). In all patients LS significantly decreased after delivery from 1.19 m/s to 0.94 m/s ($P < 0.001$). Of note, in multivariate analysis, LS was an independent predictor for the outcome of pregnancy in all patients with an odds ratio (OR) 5.442 (3.01–6.82) and cut-off value of 1.21 m/s. In a subgroup analysis of patients with established chronic liver disease, mean LS was 1.57 m/s (±0.66) and 44% (n = 26) of the patients had hepatic decompensation in the form of hepatocellular jaundice (n = 8), ascites (n = 9) and variceal bleeding (n = 6). In multivariate analysis, LS, platelet, albumin and bilirubin were independent predictors of decompensation post-delivery and the OR for LS was 6.141 (4.32–7.98). Noteworthy, the optimal cut off value of LS to predict hepatic decompensation post-delivery was 1.36 m/s with AUROC of 0.827.
Conclusion: LSM using ARFI is feasible and safe during pregnancy. Hepatic decompensation post-delivery in cirrhotic pregnant patients could be predicted by LSM using ARFI.

SAT264
Reliablility criteria will discriminate accuracy of blood liver fibrosis tests
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Background and Aims: In liver fibrosis staging, reliability criteria have been well described for liver biopsy and elastography but not for blood tests (BT). Our aim was to develop reliability criteria for liver fibrosis BT.
Method: The principle was to develop intrinsic reliability based on the composite markers of BT. We hypothesized that BT reliability depends on homogeneity between markers. We developed a homogeneity index based on the impact of each marker on the BT score. Then, we developed a reliability score (RS) by logistic regression including BT markers, homogeneity index and etiology. The outcome was the accuracy of FibroMeter (FM2G including 8 markers) for Metavir fibrosis (F) staging with liver biopsy as reference. 4981 patients (pts) were recruited.
Results: The derivation population included 3505 pts; age: 49 ± 13 yrs, 66.2% males, etiology: virus: 66.0%, NAFLD: 17.4%, alcohol: 16.7%; Metavir: F0: 8.2%, F1: 36.5%, F2: 25.1%, F3: 15.6%, F4: 14.6%; FM2G characteristics were: homogeneity index: 86 ± 8%, accuracy: 81%, RS: 81 ± 13%. The FM2G RS AUROC for accuracy (F staging) was 0.70 and the RS was well calibrated (Spearman's $r = 0.27$, $p < 0.001$). RS was classified into 3 reliability classes: low, fair and high. FM2G accuracy was, low RS (10% pts): 48%, fair RS (20% pts): 73%, high RS (70% pts): 87% ($p < 0.001$). FM2G AUROC for cirrhosis increased from 0.88 in all pts to 0.92 in 70% of pts with high RS. In a validation population of 1476 pts with Fibroscan, FM2G accuracy was, low FM2G RS (12% pts): 44%, fair RS (26% pts): 74%, high RS (62% pts): 87% ($p < 0.001$). In high FM2G RS, FM2G and Fibroscan had similar AUROC for cirrhosis at 0.93 ($p = 0.910$). Considering reliability criteria of Fibroscan (Hepatology 2013), AUROC for cirrhosis was, FM2G & Fibroscan respectively, low Fibroscan reliability: 0.87 & 0.82 ($p = 0.324$), fair: 0.84 & 0.90 ($p = 0.007$), high: 0.92 & 0.95 ($p = 0.117$). Finally, we deduced a sequential algorithm using first FM2G in high FM2G RS (62% pts) then Fibroscan in low or fair FM2G RS; accuracy increased from 78% for FM2G to 83% for algorithm ($p < 0.001$).

Algorithm accuracy was according to its own reliability classes (provided by FM2G and Fibroscan): low reliability (0.6% pts only): 44%, fair (11.5% pts): 68%, high (88% pts): 85% ($p < 0.001$).
Conclusion: Intrinsic reliability can be determined in blood tests, especially if they include many markers. This is useful for clinical practice since reliability score highly discriminates accuracy. Thus, FM2G BT is as accurate as Fibroscan for cirrhosis in 2/3 of patients with highly reliable BT.

SAT265

The usual blood liver markers provide a performant fibrosis test thanks to artificial intelligence

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Background and Aims: The usual liver fibrosis blood tests are constructed for a single target, usually significant fibrosis. The accuracy can be increased by multi-targeting different fibrosis stages. We have improved the multi-targeting thanks to Artificial Intelligence (AI). We hypothesized that AI could make indirect tests, including only indirect markers, as accurate as direct or mixed tests, including only or partially direct markers. Our goal was to compare the accuracy of classical single-targeted tests with a new multi-targeted indirect test.
Method: We compared the accuracy of 8 published single-targeted tests (indirect, direct or mixed) with a new multi-targeted test developed by AI, called FIBS-MT. It included 6 indirect markers (AST, ALT, INR, platelets, urea adjusted on sex and age). FIBS-MT was compared to the single-targeted test including the same 6 markers called FIBS-ST. Thus, the comparison of the 2 FIBS tests reflects the gain brought by AI. The FIBS tests were derived in 1013 patients with chronic hepatitis C and were compared in a validation population of 3206 patients with CLD of various etiologies. FIBS tests were compared to APRI, Fib4, Hepascore, FibroMeters (FM) 2G and 3G in 2796 patients, Fibrotest in 1461 patients, NAFLD fibrosis score (NFS) and ELF in 410 patients with NAFLD. The reference was Metavir or Kleiner fibrosis stages by liver biopsy. AUROCs for 3 fibrosis targets were compared by the Delong test: significant fibrosis ($F \geq 2$) severe fibrosis ($F \geq 3$) or cirrhosis (F4).
Results: 1/Comparison between indirect tests: all 3 FIBS-MT AUROCs were significantly higher than FIBS-ST, Fib4 and APRI, e.g. for $F \geq 3$: 0.83, 0.80, 0.79, 0.74 respectively ($p < 0.001$). 2/Comparison with mixed tests: FIBS-MT AUROC was significantly lower than FM2G or FM3G for significant fibrosis ($F \geq 2$) but not significantly different for $F \geq 3$ and F4, e.g. for $F \geq 3$: 0.83, 0.84, 0.82, respectively ($p > 0.05$). FIBS-MT AUROCs were not significantly different from Hepascore or Fibrotest for $F \geq 2$ and F4 but significantly higher for $F \geq 3$. 3/In NAFLD evaluated by F Kleiner, AUROCs of FIBS tests were not significantly different from ELF or NFS (except significantly higher vs NFS for $F \geq 3$), e.g. for $F \geq 3$: 0.77, 0.77, 0.80, 0.71, respectively (FIBS-MT vs NFS: $p < 0.037$, FIBS-ST vs NFS: $p = 0.025$).
Conclusion: The multi-targeting by AI provides an indirect test that is most accurate than the classical indirect tests and as accurate as the current mixed or direct tests for the main diagnostic targets (severe fibrosis or cirrhosis). FIBS-MT could be automatically provided by standard liver work-up.

SAT266

A gut microbiota and liver co-metabolized biomarker to monitor liver cirrhosis progression with different etiologies in humans

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Background and Aims: As cirrhosis is the most important and independent predictor of adverse outcomes in a variety of chronic liver diseases, we aimed to find the shared biomarker(s) related to liver cirrhosis of different etiologies.
Method: A total of 676 patients with three liver diseases, namely drug-induced liver injury (n = 184), autoimmune liver disease (n = 301), alcoholic liver disease (n = 141), and viral hepatitis (n = 50) from two centers were included in this study to screen for cirrhosis-related biomarkers using serum metabolomics.

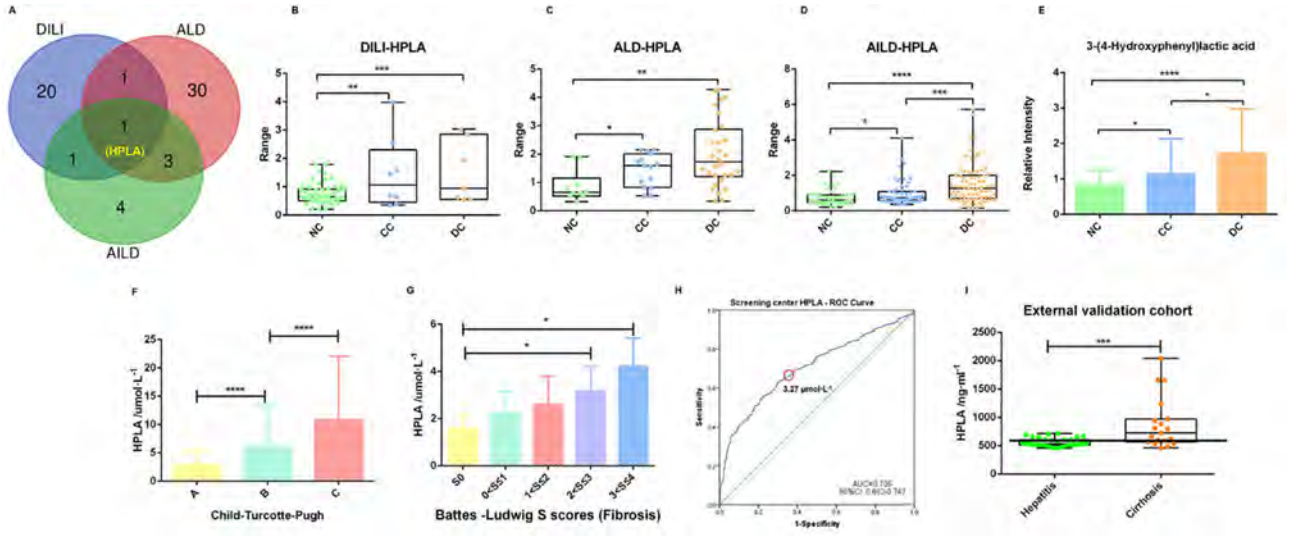

Figure: (abstract: SAT266): **A**, the Venn diagram shows the shared metabolite(s) related to cirrhosis among the different liver diseases (DILI, ALD, AILD). **B-E,** the increasing trends of HPLA along with the progression from non-cirrhosis to decompensation cirrhosis in DILI, AILD, ALD, and internal validation cohort respectively. **F** shows significant correlation between HPLA content and CHILD grades. **G** demonstrates the HPLA content increased along with the raise of Battes-Ludwig grades. **H,** Non-cirrhosis and cirrhosis groups are well separated by HPLA in screening center. The cutoff value is set at 3.27 $\mu mol \cdot L^{-1}$

Results: At the screening center discovery cohort, we separately screened for cirrhosis-related biomarkers using two strategies that did not differentiate or differentiated the three etiologies, of which only one cirrhosis biomarker, 3-(4-hydroxyphenyl) lactic acid (HPLA) was shared by the three liver diseases. Serum HPLA levels increased significantly with the progression of liver disease from non-cirrhosis stage to compensated and decompensated cirrhosis, regardless of different etiologies. This finding was subsequently verified in the internal validation cohort. By the cutoff value (3.27 μmol·L-1) of serum HPLA content, patients with cirrhosis were identified in an external prospective cohort with discrimination sensitivity and specificity of 68.42% and 61.76%, respectively. Further analysis revealed that serum HPLA content was significantly and positively correlated with either CHILD grade or MELD score in patients with different types of liver disease, and positively correlated with Battes-Ludwig fibrosis grade in liver biopsy.
Conclusion: Serum HPLA is a shared cirrhosis biomarker to monitor the progression of cirrhosis in chronic liver diseases.

SAT267

Serum metabolic biomarkers for the differential diagnosis of distal cholangiocarcinoma and pancreas ductal adenocarcinoma

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Background and Aims: The accurate diagnosis of adenocarcinomas located in the head of the pancreas -distal cholangiocarcinoma (dCCA) and pancreas ductal adenocarcinoma (PDAC)-, represents a clinical challenge since both types of tumors share symptoms and they cannot be distinguished by imaging techniques. At present there are no accurate serum biomarkers that allow early and differential diagnosis of these tumors. Omics technologies facilitate the profiling and analysis of disease-specific signatures and are powerful sources of candidates. The aim of this study was to determine serum metabolomics profiles in patients with dCCA or PDAC to identify novel biomarkers for the early and differential diagnosis.
Method: Chloroform/methanol and methanol extracts were obtained from the serum of patients with diagnosis of dCCA (n = 34) or PDAC (n = 38) confirmed by histopathology, attended in the University Hospitals of Donostia and Salamanca, and healthy individuals (n = 25) divided in two cohorts. Ultra-high performance liquid chromatography coupled to mass spectrometry (UHPLC-MS) was used to determine amino acids and lipids.
Results: A total of 484 metabolites in serum samples were identified in both cohorts and included in the univariate and multivariate data analyses. Compared to controls, serum samples of patients with dCCA and PDAC had higher levels of several metabolites, mainly triglycerides, diglycerides and bile acids in dCCA and triglycerides, diglycerides and diacylphosphatidylethanolamines in PDAC. Fewer changes were found between the circulating metabolomes of dCCA and PDAC, although several species of phosphatidylethanolamines (PE), lysophosphatidylethanolamines and triglycerides were more elevated in PDAC than in dCCA.
Among other metabolites, glutamic acid and aspartic acid distinguished tumors from controls with an AUC>0.91 and 0.94, respectively. To determine a predictive model for the discrimination between patients with dCCA and PDAC based on circulating metabolites both cohorts were merged and divided into three cohorts: training (70%) and validation (20%) for cross-validation and parameter optimization and test (10%) for blind validation. A logistic regression model with six metabolites [PC(17:0/0:0), PI(18:0/20:3), 12-HETE, PE(0:0/16:0), hydrocortisone and phenylalanine] was found, with an AUC of 0.92 in training, 0.84 in validation and 0.85 in test cohorts.
Conclusion: Specific panels of serum metabolites can be useful to distinguish dCCA from PDAC. Validation of the clinical usefulness of these biomarkers in further prospective studies is granted.

SAT268

Proteomic identification of serum factors that correlate with reduction of HVPG following curative treatment for hepatitis C virus infection

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Background and Aims: Estimation of portal hypertension through measurement of the hepatic venous portal pressure gradient (HVPG) is the best predictor of clinical outcome in advanced chronic liver disease. Several non-invasive markers (NIMs) have shown good accuracy in identifying clinically significant portal hypertension (CSPH: HVPG ≥ 10 mmHg). What is missing are NIMs that can predict reductions in HVPG. The aim of this study is to evaluate whether blood-based proteomic biomarkers are able to detect reductions in HVPG in patients with cirrhosis from Hepatitis C virus (HCV) after achieving sustained virologic response at 24 weeks post treatment (SVR24).
Method: This is a retrospective analysis of prospectively collected blood samples from patients with HCV cirrhosis, treated with direct acting antivirals. The study was IRB-approved and informed consent was obtained. Patients were from a single centre in Spain. Patients had HVPG ≥10 mmHg at baseline and a repeat measurement at SVR24. Blood samples were also taken at baseline and at SVR24. We conducted a proteomics-based study on serum samples using Somascan™, an aptamer-based technology that measures ~4500 human proteins. We determined proteins that correlate with reductions in HVPG in our patient population.
Results: Forty patients were included. Mean age was 66 years, 58% women, mean Child-Pugh score of 5 and mean HVPG of 14 mmHg (range 10 mmHg–20 mmHg). All patients achieved SVR. HVPG decreased by a mean of 2.1 mm Hg (95%CI: −3.5, −0.5; p = 0.008) from baseline. Heatmap and cluster analysis showed that the patients were grouped based on hemodynamic response to treatment. We performed Spearman correlation analysis for each of the ~4500 proteins versus change in HVPG for all 40 patients. The correlation with decrease in HVPG for all patients was 0.49 increasing to 0.77 for

responders (decrease to ≤10 mm Hg or reduction of ≥20% from baseline). To identify a proteomic signature that correlated with HVPG reduction, we performed a 10-fold cross-validated LASSO regression. We identified 14 proteins (SOMAmers™) with coefficients above 0.4, which were previously associated with either chronic liver disease progression or HCV treatment response.
Conclusion: We used a proteomic platform and machine learning algorithms to identify proteins that correlate with clinically significant decreases in HVPG. The utility of these factors as predictive biomarkers for the improvement of portal hypertension will require data from studies in larger population of patients.

SAT269

Genome-wide association study (GWAS) of circulating liver enzymes identifies >300 novel variants with distinct tissue expression patterns and gene set enrichment

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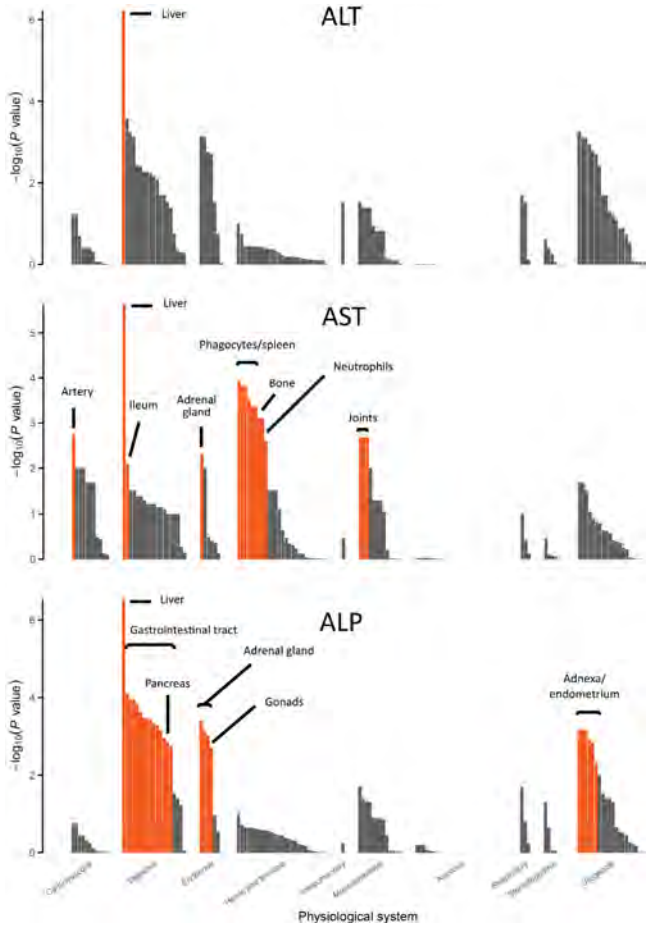
Background and Aims: Alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) are liver enzymes frequently used as indicators of liver pathology. Liver enzyme levels are partially genetically-determined, but the genetic etiology underlying this variation remains incompletely understood. We aimed to evaluate the genetic underpinning of liver enzyme levels with a cohort nearly ten times the size of the last such GWAS.



Method: We conducted a GWAS of inverse normally-transformed ALT, AST, or ALP controlling for age, sex, and principal components in >390,000 white individuals from the UK BioBank (>20,717,468 imputed single nucleotide polymorphisms [SNPs]), followed by meta-analysis with ALT, AST, or ALP GWAS results from >130,000 individuals of Japanese ancestry from BioBank Japan (5,951,600 imputed SNPs) using METAL. We characterized genome-wide significant ($P < 5 \times 10^{-8}$) SNPs using unbiased analyses including DEPICT and phenome-wide association study (PheWAS).
Results: We identified 176 total independent (163 novel) ALT, 205 (195) AST, and 221 (204) ALP SNPs. These variants represented 384 independent loci and 157 alleles affected >1 liver enzyme at genome-wide significance. Coheritability was higher between ALT and AST (0.67) than between ALT and ALP (0.24) or AST and ALP (0.21; $p < 0.0001$ for both comparisons). DEPICT analyses showed that the liver was the most enriched tissue for all three traits' associated genes. While ALT-implicated genes were relatively liver-specific, AST-implicated genes were expressed widely including in white blood cells, artery, adrenals, and joints, and ALP-implicated genes were expressed throughout the gastrointestinal tract and sex organs (Figure). Gene sets enriched among all three liver enzyme SNPs include lipid metabolism, retinoid X receptor, carbohydrate metabolism, and complement/coagulation cascades. While ALP-specific pathways included other metabolic pathways such as steroid synthesis, as well as intestinal absorption, AST-specific pathways were notable for several cytokine signaling cascades and lysosome function. PheWAS found that SNPs affecting all three liver enzymes altered risk of metabolic disease and cholelithiasis.
Conclusion: We identified >300 novel alleles that elevated ALT, AST, or ALP in UK BioBank and BioBank Japan. These variants identify genes with distinct tissue and gene set enrichment and implicate different aspects of normal liver physiology and pathophysiology.

SAT270

Virtual touch quantification using acoustic radiation force impulse technology versus transient elastography for the non-invasive assessment of liver fibrosis in patients with chronic hepatitis B or C using liver biopsy as gold standard

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Background and Aims: Our aim was to assess the diagnostic performance of Transient Elastography (TE) and Virtual Touch Quantification (VTQ), a point Shear Wave Elastography (pSWE) technique using Acoustic Radiation Force Impulse (ARFI) technology for liver fibrosis assessment, as compared to percutaneous liver biopsy (LB) in patients with chronic hepatitis B or C.
Method: We analyzed 157 patients with reliable liver stiffness (LS) measurements (80 with HBV and 77 with HCV chronic hepatitis) in which we compared TE and VTQ to the LB performed during the same session (evaluated according to the Metavir scoring system: F0-F4). LS was assessed by TE (FibroScan, EchoSens, Paris, France) and VTQ using Siemens Acuson S2000TM ultrasound system (Siemens AG, Erlangen, Germany). We defined reliable LS measurements the median value of 10 measurements with an IQR/M < 30% for both TE (obtained using the M probe) and VTQ. The areas under receiver operating characteristic curve (AUROC) were used to assess the diagnostic performance of TE and VTQ. Correlation analysis was used to determine the relationship between LSM values and liver histology.
Results: On LB, from the 157 patients, 31 (19.7%) had F0, 35 (22.3%) had F1, 43 (27.4%) had F2, 28 (17.8%) had F3 and 20 (12.8%) had F4. A strong, linear correlation (Spearman r = 0.82; $p < 0.0001$) was found

between TE and VTQ measurements. Also, we found a strong and significant correlation between TE and liver histology ($r = 0.74$, $p < 0.0001$) and between VTQ and liver histology ($r = 0.70$, $p < 0.0001$). By comparing the AUROC curves, TE and VTQ had similar predictive values for the presence of $F \geq 1$ Metavir : AUROC TE = 0.847, AUROC VTQ = 0.838 ($p = 0.867$); $F \geq 2$ Metavir : AUROC TE = 0.805, AUROC VTQ = 0.862 ($p = 0.151$); $F \geq 3$ Metavir : AUROC TE = 0.883, AUROC VTQ = 0.880 ($p = 0.949$) and for $F = 4$ Metavir : AUROC TE = 0.954, AUROC VTQ = 0.974 ($p = 0.192$). For rulling in significant fibrosis ($F \geq 2$) the optimal cutoff value was 5.5 kPa for VTQ (Se = 87.9%, Sp = 72.7%, PPV = 81.6%, NPV = 81.4%) and 7 kPa for TE (Se = 72.5%, Sp = 80.3%, PPV = 83.5%, NPV = 67.9%). For rulling out cirrhosis ($F = 4$) the optimal cutoff value was 8.9 kPa for VTQ (Se = 90%, Sp = 90.5%, PPV = 58.1%, NPV = 98.4%) and 10.7 kPa for TE (Se = 90%, Sp = 91.2%, PPV = 60%, NPV = 98.4%).

Conclusion: Both methods, TE and VTQ (pSWE) offer excellent diagnostic accuracy for liver fibrosis assessment in patients with chronic hepatitis B or C, with similar performance.

SAT271

Quantitative magnetic resonance cholangiopancreatography imaging in patients with primary sclerosing cholangitis - feasibility and preliminary analysis for prediction of clinical outcomes

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Background and Aims: Magnetic resonance cholangiopancreatography (MRCP) is a non-invasive imaging technique commonly used for the evaluation of biliary disease. Despite its widespread use, MRCP relies on subjective assessments, lacking robust quantitative metrics and cannot predict the onset of liver related events. Quantitative MRCP (MRCP+^{TM}) is a novel technique that can quantitively assess biliary tree metrics. This study sought to understand the utility of MRCP+ in predicting clinical outcomes for primary sclerosing cholangitis (PSC).

Method: In this retrospective study, 35 PSC patients (69% Male; 82.9% Caucasian; mean age 54 years [7–70]) underwent standardised MRCP imaging. Images were post-processed using MRCP+ software, which enhances and quantifies the tubular biliary structures. The underlying algorithms combine an intelligent path search algorithm and novel duct modelling algorithms. The duration (in days) between the date of clinical event (liver transplant surgery or death) and the date of MRCP scan was calculated for the survival analysis; the Cox regression and Kaplan-Meier Estimator have been used to investigate the utility of MRCP+ derived metrics in predicting clinical outcomes.

Results: From the 35 patients, 13 (37%) PSC patients experienced a clinical event. The Cox survival analysis showed that MRCP+ derived metrics (the number of dilated ducts, the number of ducts with stricture or dilatation, and the total length of abnormal ducts) predicted the probability of a clinical outcome (either liver transplantation or death) ($p = 0.048$, 0.046 and 0.037, respectively). Optimal thresholds (of 12, 2 and 102 mm, respectively) of the above-mentioned MRCP+ metrics were calculated and applied. Low-risk patients (values below cut-off) had significantly higher liver-event-free survival than high-risk patients (values above cut-off) ($p = 0.012$, 0.0041 and 0.0027, respectively) (Figure 1).

Conclusion: Quantitative MRCP (MRCP+) has been used for the first time to predict clinical outcomes in patients with PSC. Further analysis with a larger sample size and comparison to risk scores such as mayo risk score and UK-PSC risk score are in progress and will be presented at the meeting.

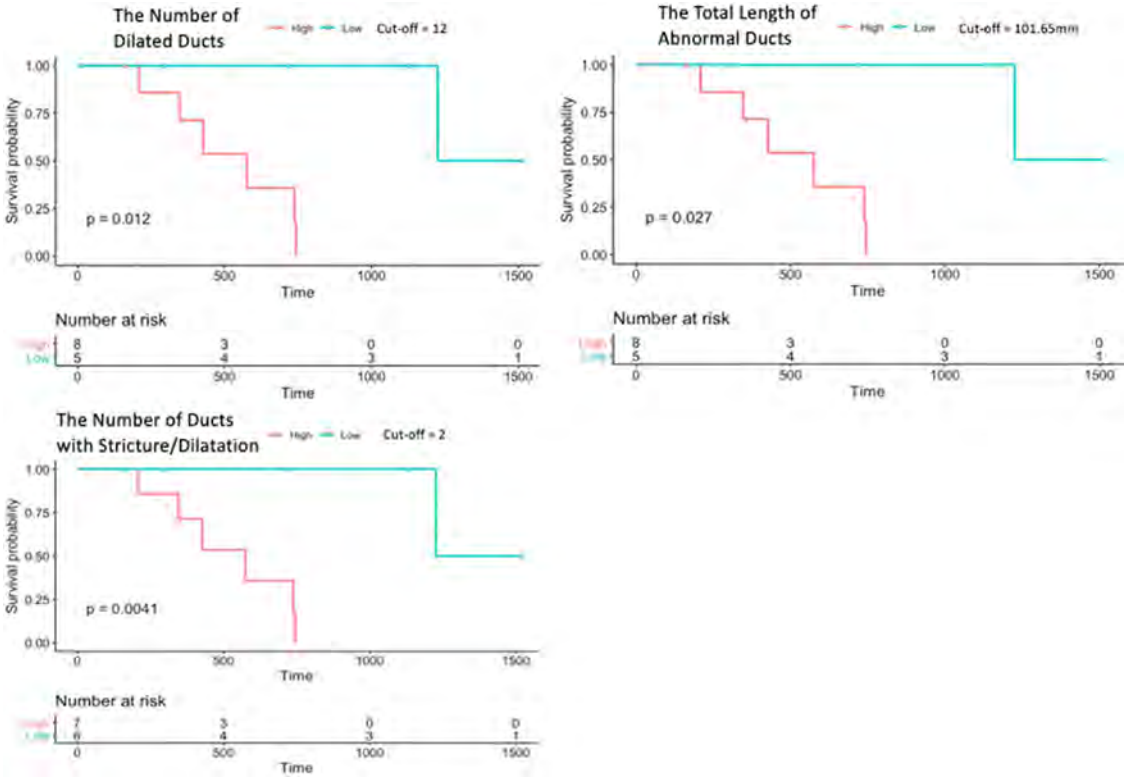

Figure: (abstract: SAT271): Kaplan-Meier Survival Curves for MRCP+ metrics.

SAT272

Two-dimensional real-time shear wave elastography and risk for de novo hepatocellular carcinoma in patients with advanced chronic liver disease

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Background and Aims: Liver cirrhosis is the most important risk factor in the development of de novo hepatocellular carcinoma (HCC) regardless of etiologies. Early non-invasive screening for cirrhosis using liver stiffness (LS) may also give information on the risk of HCC. This is the large-scale international multicenter study to evaluate clinically relevant end-point in liver cirrhosis using two-dimensional real-time shear wave elastography (2D-SWE).

Method: Chronic liver disease patients were screened from 15 centers from Europe and China. Besides, they were included if they had valid 2D-SWE at baseline. Clinical and laboratory parameters were assessed at baseline. We conducted the follow-up regularly after first assessment. De novo HCC was diagnosed according to the 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Univariate and multivariate logistic regression model were used to explore risk factors of de novo HCC. Area under the receiver operating characteristic curve (AUROC) and Youden index were analyzed to find out the optimal cutoff for LS with SWE.

Results: A total of 1881 were included in the study with a median follow-up of 2.3 years. Most of the patients were male (61.5%) and middle-aged (median [IQR]: 55 [45–63] years). Non-alcoholic fatty liver disease (31.0%) accounted for the major etiology, followed by viral hepatitis (15.8%) and alcoholic liver disease (8.6%). Eighty-five (4.5%) patients were diagnosed with de novo HCC, and had a doubled median 2D-SWE value than those without HCC (22.0 vs. 11.1, $p < 0.001$). LS value of SWE (odds ratio [OR]: 1.013, 95% confidence interval [CI]: 1.002–1.024, $p = 0.022$) was independently associated with developing de novo HCC in multivariate analysis after adjusting for age, creatinine, INR, platelets and bilirubin. The AUROC of 2D-SWE was 0.701 (95%CI: 0.657–0.746). At the best cut-off of 13.6 kPa, a 78% of sensitivity and a 60% of specificity were obtained, with a negative predictive value of up to 98%. Patients with LS values above the cutoff (>13.6 kPa, OR: 2.040, 95% CI: 1.122–3.709, $p = 0.019$) and lower platelet counts were markedly associated with de novo HCC (Figure).

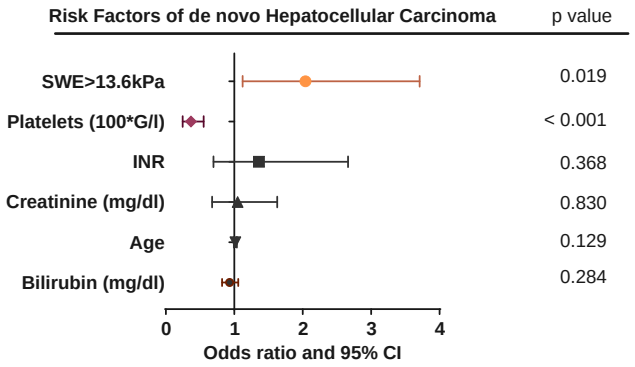

Figure: (abstract: SAT272)

Conclusion: The LS of SWE is associated with de novo HCC with the optimal cutoff of 13.6 kPa. If further confirmed in other populations, SWE could be used as a convenient auxiliary diagnostic tool to assess the risk of de novo HCC.

Public Health

SAT273

Progress in hepatitis C testing as a part of the hepatitis C elimination program in Georgia

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Background and Aims: The country of Georgia, with a population of 3.7 million and an estimated 150,000 adults with chronic hepatitis C virus (HCV) infection, initiated the world's first national hepatitis C elimination program in April 2015. Through the elimination program, screening for hepatitis C is available to all citizens free of charge. The aim of this analysis is to describe progress in hepatitis C testing as part of hepatitis C elimination program.

Method: This analysis utilizes data from the national screening registry and treatment databases linked by national ID, and 2014 general population census. An information system was created to collect data from the elimination program utilizing the national ID to monitor and evaluate program performance and surveillance.

Results: As of November 10, 2019, 1,628,452 adults have been tested for hepatitis C (56.9% of the adult population), of whom 125,016 (7.7%) were anti-HCV positive. In 2015 the positivity rate averaged 27.0%, but has fallen to 4.4% in the first half of 2019. Overall, 98,134 individuals received viremia testing, of whom 80,074 (81.6%) were found to have chronic HCV. Screening rates are similar for men and women (55.9% vs. 57.9%, respectively). Among men screening rates are highest among those aged ≥60 (64.2%) and lowest among those aged 18–29 (51.7%). The overall positivity rate for adult males is 12.4%. The highest positivity rate is seen in men aged 30–59 (18.6%). Among women screening rates are highest among those (60.7%) aged 18–29 (60.7%) and lowest among those aged 30–59 (56.4%). The overall positivity rate for adult females is 3.7%. The highest positivity rate is seen in women aged ≥60 (5.3%).

Conclusion: The overall anti-HCV prevalence was higher in males and among those aged 30–59 years. The anti-HCV positivity rate has been declining since the launch of the HCV elimination program in April 2015. Although significant progress has been made, a substantial proportion of infected people need to be identified, confirmed, and linked to care.

SAT274

Evaluation of hepatitis B virus (HBV) epidemiology, vaccine impact and treatment eligibility: a census-based community serological survey in Blantyre, Malawi

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Background and Aims: Hepatitis B is the leading cause of cirrhosis and hepatocellular carcinoma in sub-Saharan Africa. To achieve WHO targets of reducing mortality by 65% by 2030, antiviral treatment programmes are needed. Epidemiological data are required to inform an effective public health response and anticipate treatment needs.
Method: Infant HBV vaccination began in Malawi in 2002. We conducted a census and serological survey in Blantyre in 2016–18. We selected individuals from the census for serosurvey participation by probability sampling. We estimated HBV prevalence using post-stratification proportional fitting to census age-sex distribution. HBsAg-positive participants were evaluated for treatment eligibility. We estimated vaccine impact by comparing HBsAg prevalence of individuals born 5 years before and after vaccine implementation.

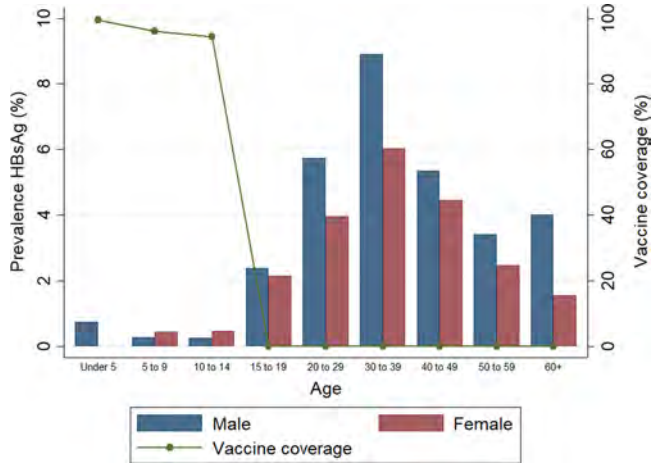

Figure: HBsAg prevalence among serosurvey participants stratified by age and sex and vaccine coverage.

Results: Of 97,386 censused individuals, 6,073 were sampled in the serosurvey and tested for HBsAg. HBV prevalence was 5.1% (95% CI 4.3–6.1) among adults and 0.3% (0.1–0.6) among children born after vaccine introduction. Three-dose vaccination coverage was 97.4% (1141/1172) in children ≤10 years. Vaccine impact was 95.8% (70.3–99.4). Treatment eligibility was assessed in 94/150 HBsAg positive adults, among whom 24 (26%) were HIV positive and 16/24 (67%) were receiving tenofovir-containing antiretroviral therapy. Among 69 HIV negative individuals, 2%, 6% and 9% were eligible for treatment by WHO, EASL and AASLD criteria respectively. Projected to the national population, 25586 (95% CI 7172–65519) people will require HBV treatment by EASL criteria.
Conclusion: In an urban township in Malawi, HBV prevalence was 5.1% among unvaccinated adults and infant HBV vaccination was associated with a vaccine impact of 96%. Among HBsAg-positive adults, one quarter were HIV-positive and 3–9% of HIV-negative adults required antiviral therapy.

SAT275

HCV in addiction care: different epidemiology, excellent treatment results

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Background and Aims: Patients treated in addiction care units (ACU) have a higher prevalence of hepatitis C virus (HCV). There is not much evidence about its access to treatment and its results. Our aim is: 1) To determine the epidemiological characteristics and results of treatment in the registered population in ACU treated with direct-acting antivirals (DAA). 2) Compare with a general cohort treated in the same period of time.
Method: 1) Inclusion criteria: population with positive RNA-HCV test treated with DAA. 2) 2 groups were analyzed: HCV population registered in ACU and/or Penitentiary Center (HACU) and general population (GP). 3) Variables: age, sex, viral genotype, fibrosis stage, response to treatment (SVR12). Using the statistical package SPSS version 25. Continuous variables as means ± SD, discrete as frequencies (%). Correlation between qualitative variables using Pearson's Chi square (significant $p < 0.05$).
Results: HACU (n = 198 patients) and GP (n = 948 patients). Mean age (interval) years: HACU 46 (24–63) and GP 53 (18–56). Men (%): HACU 92%, GP 61%. Genotypes (1a/1b/2/3/4)%: HACU (42.3/9.5/0/29.6/8.46) vs. GP (30.2/38.7/2.11/18.5/9.07). 16 patients (8 from each group) were not genotyped. Fibrosis stage was determined by hepatic elastography and cirrhosis was defined by obvious clinical and/or image data. The distribution by stages (F0-1/F2/F3/F4)% was: HACU (31.2/20.6/18/29.6) vs. GP (27.3/22.7/16/32.5). Fibrosis stage was not established in 1 patient of the HACU group and 14 of the GP. We found no significant differences when comparing sex and genotype, age and fibrosis stage, genotype and fibrosis stage within the patients of the HACU group.
When comparing HACU against GP significant differences were observed by genotype (p: 0.001) observing a higher prevalence of genotype 3 in HACU. However, no significant differences were observed by fibrosis stage (p: 0.55).
We have the result of treatment in 189 patients of the HACU group (4 patients lost were recovered and sustained virological response -SVR12- was confirmed and 2 who abandoned therapy are currently in re-treatment). The SVR12 for ITT was 91.4% in HACU vs. 95.2% in GP; in the PP analysis SVR 12 was 100% in HACU vs. 99.5% in GP.

Conclusion:

1. In relation to GP treated with DAA, HACU population is younger, with male predominance and different genotype distribution (1a most frequent, 3 more represented).
2. More than 40% of the patients in the HACU group have advanced stage of fibrosis or cirrhosis.
3. SVR12 is excellent in both groups with proper strategies that avoid tracking losses.

SAT276

Modelling the cost of hepatitis C virus transmission in Pakistan

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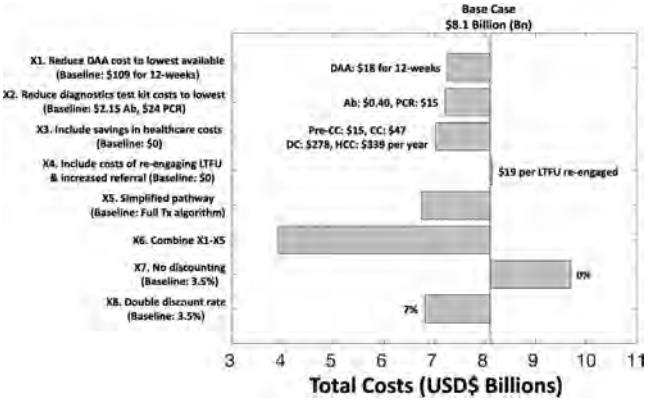
Background and Aims: Pakistan has the world's second-largest hepatitis C virus (HCV burden). The World Health Organization (WHO) HCV-elimination strategy advocates for a reduction in HCV incidence by 80% by 2030, but little is known about how this could be achieved and the costs of doing so in Pakistan.

Method: A general population HCV transmission, screening, and treatment model was developed and calibrated using available data from Pakistan, incorporating cost data on diagnostics and HCV treatment. We modelled the impact and costs of alternative strategies for scaling-up screening and HCV treatment to determine what is needed and the resulting costs of achieving the WHO HCV incidence target in Pakistan.

Results: One-time screening of 90% of the 2018 population by 2030, with 80% referral to treatment, leads to 14 million individuals being screened and 350,000 treated annually, decreasing incidence by 27% over 2018–2030. Prioritising screening to higher prevalence groups (people who inject drugs (PWID) and adults >30 years) and introducing re-screening (annually for PWID, otherwise 10-yearly) increases the number screened and treated by half and decreases incidence by 51%. Decreasing HCV incidence by 80% requires doubling the primary screening rate, increasing referral to 90%, re-screening the general population every 5-years, and re-engaging those lost-to-follow-up every 5-years. This could cost USD$8 billion, reducing to USD$4 billion with lowest costs for diagnostic tests and drugs, including healthcare savings, and implementing a simplified treatment algorithm.



Conclusion: Pakistan will need to invest up to 9% of their yearly health expenditure to enable sufficient scale-up in screening and treatment to achieve the WHO HCV-elimination target for incidence.

SAT277

The best strategy for retrieval of hepatitis C patients lost to follow up: randomized clinical trial

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Background and Aims: In order to achieve hepatitis C virus (HCV) WHO 2030 elimination goals, stakeholders should increase the rate of new diagnoses and linkage to care those lost to follow-up. Different strategies have been implemented to overcome barriers related to diagnosis, but there is a lack of studies approaching the best retrieval strategy for those lost to follow-up . Our aim was to evaluate the efficacy and effectiveness of two different strategies for retrieval of previously diagnosed HCV patients lost to follow-up, which is key to reach microelimination in our healthcare area.

Method: from data files of laboratory and microbiology charts since 2005 we identified patients with positive HCV antibodies without RNA request or positive RNA without a subsequent negative RNA lost to follow-up . Those still alive with currently available data for contact (by phone and mail) and in our healthcare area were randomly assigned (NCT04153708) (n = 176 each arm) in any of the two strategies: 1) phone calls to provide patients an appointment and 2) invitation mail letter with a scheduled appointment. We evaluated efficacy as the rate of patients who turn up for the appointment in each strategy and effectiveness taking into account the use of resources. Statistical analysis was performed with Chi2, t-student and Poisson regression. The study was approved by the local Hospital Ethics Committee.

Results: 352 subjects were included in both strategies (74.6% men, mean age 51.3 ± 13.3 years-old) with no differences between groups. In strategy 1, 8.7% of the patients were excluded due to change of the holder of the phone line, whereas, in strategy 2, 11% of the letters failed to reach the address and were returned. Eventually, in strategy 1, 42.4% did not answer the phone call and 10.2% were not interested to participate. The rate of patients that turned up for the scheduled appointment was higher in the strategy 1 (median 9 days, [1–17])

than in strategy 2 (median 12 days, [11–13]) (46.5% vs 28.2%, p = 0.033). The number of phone calls needed for one retrieval was 11:1 in the strategy 1, whereas the number of letters which correctly reached the address needed for one retrieval was 4:1 in strategy 2 (OR 3.03, IC 95% [1.653–5.549], p < 0.001).
Conclusion: the retrieval of patients with HCV diagnosis lost to follow-up is feasible through both strategies. However, our results suggest that the strategy of phone calls seems to be more effective, although the invitation mail letter is more efficient.

SAT278

Is hospital admission an ideal condition for HCV screening? A survey from the Venetian area (north-east of Italy)

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Background and Aims: The best strategy to bring out the hidden chronic HCV infection in order to plan the virus elimination remains uncertain. Current guidelines recommend screening in high risk populations, but other strategies should be defined according to the local HCV epidemiology. In Veneto Region (North-East of Italy) the actual prevalence of HCV infection is not well-known but is estimated between 0.5–1% of the general population, that seem a too low value to justify a community screening in terms of cost-benefit. Nevertheless hospitalized patients may represent an ideal population for HCV screening and for referral to treatment, but few data are available in this specific setting of subjects. Aim of this study was to determine the prevalence of HCV infection in unselected hospitalized subjects in the Venetian area, North-East of Italy, in order to identify hidden infection and to plan a micro-elimination strategy of the virus.
Method: All patients consecutively admitted to the surgical departments of the "dell'Angelo" Hospital, Venezia-Mestre, from 01/01/2017 to 30/06/2018, were tested for anti-HCV antibodies (CMA Abbott laboratories). In case of borderline values, a confirmatory RIBA test (INNOLIA HCV) was carried out. Positive patients were tested for HCV-RNA (RT-PCR Abbott laboratories) and HCV-genotype
Results: Overall, 11166 patients were tested at admission (40.4% males). 237 subjects resulted anti-HCV positive, with a prevalence of 2.1%. The prevalence was significantly higher in men (2.5%) than in women (1.7%) and increased with age (from 0.6% in 15–30 years patients to 2.8% in 51–60 and over 70 years patients). The highest prevalence was observed in Vascular Surgery (3.5%), Traumatology (3.4%) and Neurosurgery (2.8%), the lowest in Gynecology (1.0%) and Urology (1.6%). HCV RNA was detectable in 66% of patients and the most represented genotype was genotype 1 (80%). The large majority of subjects (70%) were unaware of their status and are now being recruited for the treatment.
Conclusion: Our data show a significant prevalence of HCV infection in hospitalized subjects, two to three times higher than that expected in the general population of the Veneto region. Screening for HCV infection in this specific setting of subjects may thus represent a simple and cost-effective strategy to identify hidden HCV-infection and for treatment referral, in order to achieve HCV micro-elimination.

SAT279

A novel microsimulation model of chronic hepatitis B (HBV): validation of HBV viral dynamics and cumulative incidence of hepatocellular carcinoma

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Background and Aims: Hepatitis B virus (HBV) is a leading cause of cirrhosis and hepatocellular carcinoma (HCC) worldwide. Existing HBV models do not simulate viral parameters. Our objective was to develop a microsimulation model of chronic HBV that incorporates dynamic changes in HBV DNA.
Method: We simulated a cohort of individuals after perinatal HBV infection, progressing through the natural history of HBV in 1 month time steps from birth until age 75 y. Simulated patients can progress through up to 4 phases of chronic HBV natural history, which are correlated with clinical outcomes: *Phase 1* eAg+ chronic infection; *Phase 2* eAg+ hepatitis; *Phase 3* eAg- chronic infection; and *Phase 4* eAg- hepatitis. Data from cohort studies informed key input parameters: initial DNA distribution; changes in DNA, conditional on HBV phase; transition rates between HBV phases; rates of sAg loss and HCC incidence, both conditional on HBV phase and HBV DNA. Model outcomes included: HBV DNA during each phase; cumulative incidence of eAg seroclearance (transition to Phase 3); cumulative incidence of sAg loss and HCC in Phases 3 and 4. We validated model-based results by visual comparison with data from the REVEAL cohort in Taiwan.

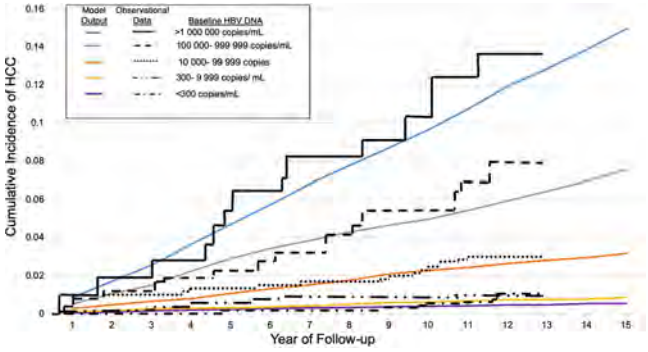

Figure: Validation of model-simulated HCC cumulative incidence in Phases 3 and 4, stratified by HBV DNA compared to observational data from the REVEAL cohort (adapted from Chen CJ, et al. JAMA 2006;295:65-73.)

Results: Consistent with published observational data, HBV DNA was highest in Phase 1 (median [IQR]: 7.98 [7.50–8.49] log copies/mL) and lowest in Phase 3 (median [IQR]: 2.79 [2.00–3.58] log copies/mL). HBV DNA showed the most fluctuations within and among simulated

subjects in Phase 2 (median [IQR]: 5.14 [3.52–6.58] log copies/mL) and Phase 4 (median [IQR]: 4.81 [3.35–6.62] log copies/mL). By the end of the simulation, 95% of the cohort achieved eAg seroclearance, as observed in the REVEAL study. Cumulative incidence of sAg loss was 30% in Phase 3 and 4, corresponding to 1.51/100 person-years (PY), with higher rates among those achieving undetectable HBV DNA. Model-estimated HCC incidence was 6.4% in Phases 3 and 4, corresponding to 319/100 000 PY, consistent with published data. HCC incidence was greater among patients with higher HBV DNA, as per observations from the REVEAL cohort [Figure].
Conclusion: This novel simulation model projects trajectories of HBV DNA, sAg loss, and HCC cumulative incidence validated to published cohort data. This model will be useful to assess the cost-effectiveness of different HBV screening, monitoring, and treatment strategies.

SAT280

Rapid test & treat programme successfully facilitating hepatitis C micro-elimination in a women's prison

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Background and Aims: Hepatitis C (HCV) is more prevalent amongst those in prison than in many other populations. However, despite significant work and investment, testing and treatment rates in many prisons have remained disappointing. We therefore developed a Rapid Test & Treat (RT&T) programme for a woman's prison with an aim to increase uptake of testing, commencement & completion of treatment.
Method: Cepheid testing was performed as an opt-out at entry into a female prison (with approximately 1500 new entrants per year) Those determined to have active infection were fast-tracked onto pan-genotypic regimens. Outcomes were compared to data from 2018 (prior to programme commencement).
Results: Rates of testing, diagnosis, and treatment are shown in the Figure. During the RT&T programme (March – October 2019) a total of 79 prisoners were commenced on treatment (with only 21 treated in the entire of 2018 - before the programme commenced). The median times from prison entry to diagnosis, and from diagnosis to treatment, were significantly decreased (from several weeks to less than 5 days). This programme, in combination with initiatives to diagnose existing prisoners, has resulted in prison micro-elimination (currently >96% prisoners tested & treated). Satisfaction with the RT&T programme was very high.

	Prior to Programme	During Rapid Test&Treat Programme
% of entrants tested at entry to prison	38.6	69.6
% of those who are positive for HCV	51.0	9.6
% of those HCV positive commencing treatment	17.9	93.8

Conclusion: Establishing opt-out point of care testing at entry to prison is feasible and results in markedly increased testing, increased treatment, shorter delays and improved satisfaction. The programme is now being rolled out to other local prisons and is a pivotal component of the regional HCV elimination programme. Further updated data including SVR rates will be available at the conference.

SAT281

Role of immigration in chronic HBV and HCV infection in our environment. Origin and characteristics of the patients

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Background and Aims: Migration is one of the most influential factors in the dynamics of hepatitis B and C epidemiology. To know the relevance of immigration in chronic hepatitis/infection by HBV (CHB) and chronic hepatitis C (CHC) in our environment and to compare characteristics of immigrants with each infection.
Method: All patients with CHB (n = 624) and CHC (n = 1405) from Jan/2014 to Oct/2019 were analyzed. Clinic and demographic variables were collected prospectively. Evaluation of liver fibrosis was performed by elastography.
Results: The proportion of immigrants was 36% (222/624) in CHB and 5% (70/1405) in CHC (p < 0,001) and was higher in incident than in prevalent cases, both in CHB [62% (124/199) vs 23% (98/425); p < 0,001] and CHC [7.4% (51/688) vs. 2.6% (19/717); p < 0,001]. Only 1 immigrant had CHB and CHC. There were no differences between immigrants with CHB and CHC in sex (male: 48% vs 53%; p = 0,08) not in HIV coinfection (2.3% vs. 1.4%;p = 1). Those with CHC were older [50 vs. 35 years; p < 0,001], consumed alcohol more frequently (13% vs. 3.3%; p = 0,009) and a higher proportion had F3-F4 (42% vs. 7.6%;p < 0,001). The main mechanism of infection was drug use (DU) in CHC (22%) and vertical/intrafamilial transmission in CHB (36%); none of the last referred DU. Immigrants with CHB came from 30 countries; the highest number of cases from Romania [ROM] (45), Senegal [SEN] (40), China [CHI] (37), Equatorial Guinea [EG] (17) and Portugal [POR] (13). Immigrants with CHC came from 22 countries; the highest number of cases from ROM (14), EG (10), Dominican Republic [DR] (7), Russia [RUS] (5) and POR (5), none from CHI or SEN. The geographic areas with the highest CHB proportion were Sub-Saharan Africa [SA] (31%), Eastern Europe [EE] (27%) and Asia (18%), while for CHC they were EE (44%), SA (14%) and Central America-Caribbean (14%). Taking into account the number of immigrants in our area and their origin, the countries with the highest proportion of CHB were EG (28%), SEN (9%), CHI (7.2%), DR (3.9%) and POR (2.9%), while for CHC they were GE (16%), RUS (3.6%), RD (1.4%), POR (0.8%) and RUM (0, 5%).
Conclusion: The role of immigration in CHB and CHC is increasing and it is significantly greater in CHB. However, immigrants with CHC have more advanced liver disease. There are important differences between both in the acquisition mechanism and patient origin. Although ROM is the country with the highest number of cases of both infections, the high proportion of patients from EG with CHB and CHC is notable.

SAT282

From stagnation to elimination: tracking hepatitis C elimination policy implementation in Europe in partnership with patient organizations

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Background and Aims: New hepatitis C virus (HCV) treatments spurred the World Health Organization (WHO) in 2016 to adopt a strategy to eliminate HCV as a public health threat by 2030. To achieve this, key policies must be implemented. In the absence of monitoring mechanisms, this study aims to assess the extent of policy implementation.
Method: Thirty liver patient organizations were surveyed in Oct 2018. They were queried on how policies were implemented in practice. Respondents received two sets of questions: 1. addressing WHO recommendations; and 2. from validated data sources verifying an existing policy in their country. Experts selected key variables from each set for inclusion into index scores. The index scores were calculated with a multiple correspondence analysis (MCA). Proxy reference countries StagNation (no policies) and ElimiNation (all policies implemented) were included to contextualize answers. In the second index, ProcrastiNation (all policies in place, but none implemented) was also included. We extracted scores for each country and standardized them from 0 to 10 (best).
Results: In total, 25 countries responded. In the WHO recommendations index, we included: microelimination in migrants, people who inject drugs, prisoners, sex workers and service integration of blood safety, harm reduction, and migrant services. The WHO MCA yielded a 1-Dimension (1D) solution explaining 75.5% of the variation. Bulgaria had the lowest score with all negative responses while 5 countries had perfect scores (Figure 1A). In the verified policy index, we included the variables: fibrosis restrictions, drug alcohol restrictions, needle-syringe program (NSP) community, NSP prison, opioid substitution therapy (OST) community, OST prison, HCV testing in prisons, and HCV treatment in prisons. The verified policy MCA yielded a 2D solution with D1 (if policies were in place) accounting for 44.3% of the variation and D2 (the proportion of policies in place that were implemented) accounting for 34.6%. Spain had the highest scores for D1 and D2, while Bosnia Herzegovina and Finland had the lowest scores for D1 and D2, respectively (Figure 1B).
Conclusion: Patient groups reported that WHO recommendations and the implementation of HCV policies is low in practice in Europe with major differences among countries. If countries are to meet HCV elimination, they need to further expand efforts, especially to vulnerable populations

SAT284

Treatment cascade of hepatitis C in a non-university hospital setting, that uses a hub-and-spoke model, in southern Switzerland

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Background and Aims: Despite the introduction of direct-acting anti-viral agents (DAA), the management of HCV (hepatitis C virus) still represents a public health challenge. Universal DAA access has been available in Switzerland since 2017. The present study aimed to describe the cascade of care of anti-HCV positive individuals in a non-university hospital setting where a decentralized approach is used.
Method: This is a retrospective study in which we collected the data of all positive anti-HCV antibodies individuals (still alive and deceased) seen at the Epatocentro Ticino since 2007 till the end of 2017. The following data were collected: age at presentation, country

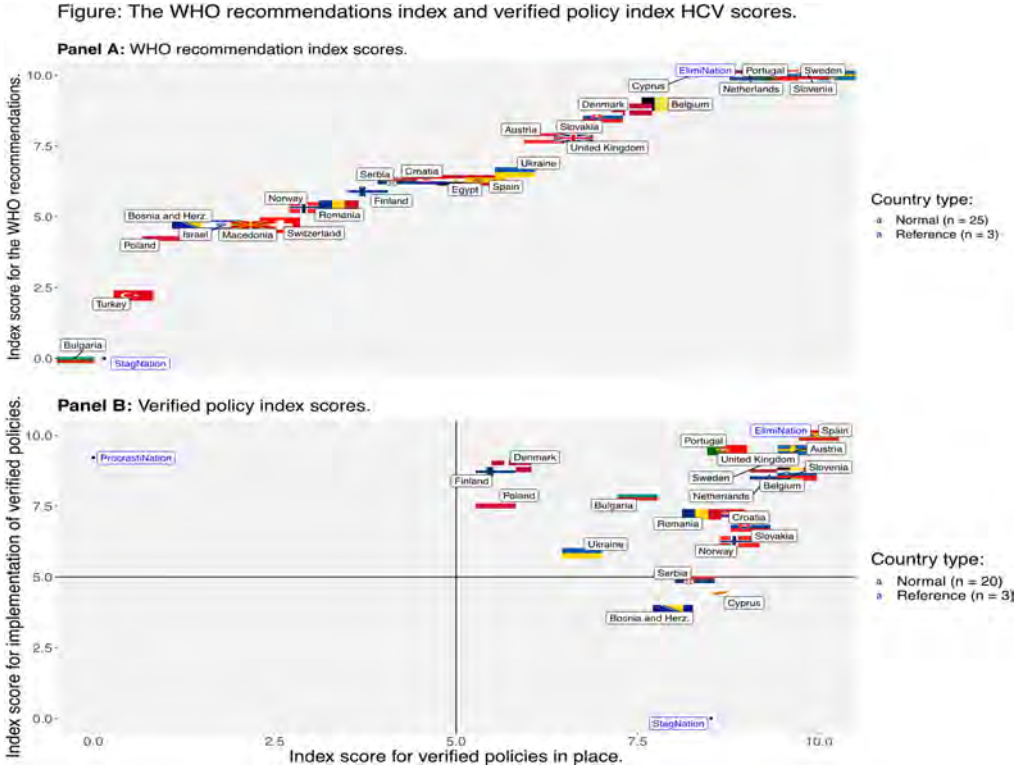
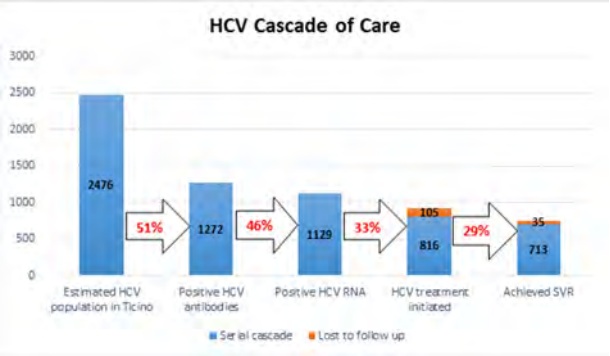


Figure: (abstract: SAT282)

of birth, fibrosis stage, mortality, anti-viral treatment status, treatment outcome, and lost to follow-up status. Two time-points have been considered for data analysis: firstly, the year of the first visit at our center and secondly, the most recent time-point the subject has been seen in our center.

Results: A total of 1272 anti-HCV positive patients were identified and included in the data analysis. Median age at the first visit was 51.0 years (IQR 44–63). A total of 1129 patients (89%) had positive HCV RNA in plasma at baseline, 136 were HCV RNA negative, 35% of them had been treated before the first visit at the center and 27% had spontaneously cleared the virus. HCV genotype distribution in the study population was: 45% genotype 1, 15% genotype 2, 22% genotype 3, 8% genotype 4, and less than 1% genotypes 5 and 6 or mixed genotypes. 446 patients (35%) had significant fibrosis at baseline, assessed by either liver biopsy (>stage F2), clinical signs of portal hypertension or liver transient elastography above 10 kPa. A total of 816 patients (72% of the patients with positive HCV RNA at baseline) had access to HCV treatment (Figure 1). Of them, 383 patients were treated by (peg)interferon and ribavirin, 633 were treated by DAA, of whom 197 received DAA as re-treatment after failure of (peg) interferon-based treatment. A total of 713 patients (87%) that had access to treatment were cured (data on treatment outcome were missing in 35 patients).



Conclusion: At least 29% (Figure 1) of the estimated HCV population in Ticino achieved sustained virological response (SVR) in the last 10 years, of whom 71% had been cured since the DAA therapies had been available. In Kantonsspital St. Gallen, characterized by a centralized model, the achievement of SVR in a similar period of time (2004–2016) was 13%. If we compare the two models, the hub-and-spoke model used by our center, has allowed the treatment and healing of more than twice as many individuals as the centralized model.

SAT285

A nurse led hepatitis C model of care in primary care and community services in Melbourne, Australia

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Background and Aims: Hepatitis C virus (HCV) testing and treatment at primary care and community based services will be a critical component of HCV elimination. We conducted an analysis of a nurse-led service at nine sites to evaluate progression through the HCV care cascade from January 2017-September 2019.

Method: People accessing services from nine sites including seven primary care services, a homeless service and a mental health service were either referred to nurses or engaged by nurses directly during regular visits. Nurses provided HCV education, testing and follow-up services. Those who tested HCV RNA positive were contacted by the nurse to discuss treatment and prescription was provided by an affiliated doctor or nurse practitioner. People with suspected cirrhosis based on transient elastography were referred to gastroenterology specialists. Logistic regression was used to examine factors associated with treatment commencement and sustained virological response (SVR) testing.

Results: A total of 688 people were referred to and/or engaged by the nurses; 564 had a HCV test of whom 420 (74%) were HCV RNA positive. Treatment was commenced by 324 (77%) with 207 (64%) prescribed by a general practitioner or a nurse practitioner. SVR testing was due for 288 by end September 2019, 174 (60%) were known to have had a SVR test, 169 (97%) were cured. Of those not cured, two were suspected reinfection, two were non-adherence and one was a relapse.

Adjusted for age, gender and Aboriginal or Torres Strait Islander status, there was no significant difference in treatment commencement among people who reported injecting drug use in the last six months (aOR 0.58, 95%CI 0.26–1.31) compared to those who did not. Compared to people seen in primary care services, treatment uptake was significantly lower among those engaged through the homeless service (aOR 0.21, 95%CI 0.08–0.51). There were no significant differences in SVR testing among those who started treatment based on injecting in the last six months (aOR 1.75, 95%CI 0.83–3.72) nor engagement through the homeless service (aOR 1.96, 95%CI 0.45–8.56).

Conclusion: A nurse-led model of care can lead to high levels of HCV treatment and cure among people attending primary care and community services. While specialist referral pathways are required for people with cirrhosis, restricting all HCV treatment to specialists is unjustified, as is restriction based on active injecting drug use. More tailored models of care are required for people attending homeless services.

SAT286

Barriers to hepatitis C virus elimination in Germany: why aren't diagnosed patients initiating therapy?

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Background and Aims: Despite the availability of effective and well-tolerated direct-acting antivirals, many patients with chronic hepatitis C virus (HCV) infection delay or never initiate treatment. This observational study compared characteristics of patients who did and did not initiate HCV treatment and identified the reasons for this according to physicians. There were no budget constraints, as reimbursement is not a barrier to treatment in Germany.

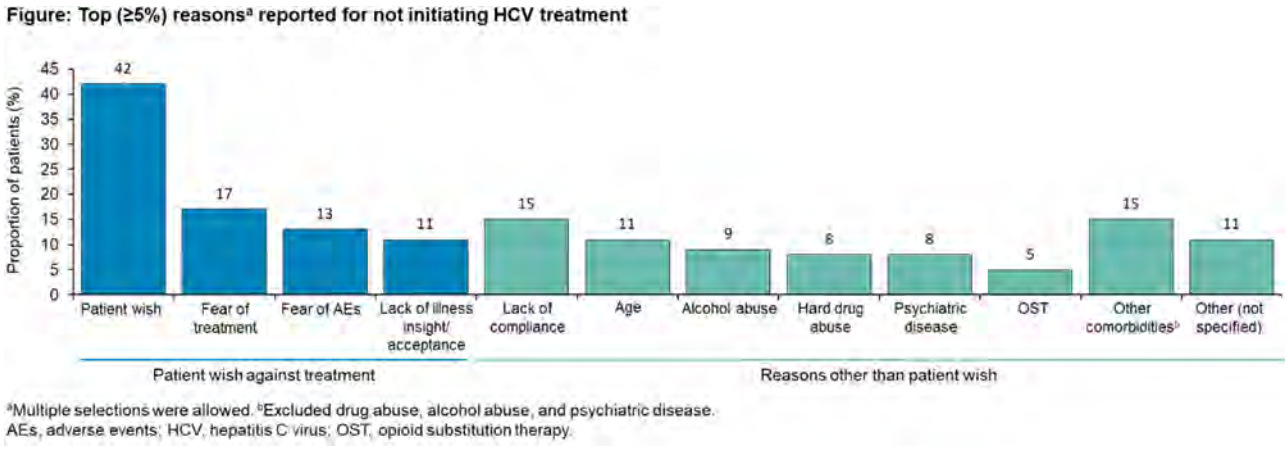

Figure: (abstract: SAT286)

Method: The CURRENT-C study was an epidemiologic, non-interventional, case-control study that identified patients with chronic HCV infection in 43 sites in Germany (1 September 2017–30 June 2018). Baseline characteristics of patients who did or did not initiate treatment were evaluated. Reasons why physicians and/or patients decided against initiating or for delaying HCV treatment were collected.
Results: Of 793 patients, 573 (72%) initiated treatment and 220 (28%) did not. Of those not initiating treatment, 88 (40%) delayed treatment and 132 (60%) had no therapy planned. In patients who did vs did not initiate treatment, 102 (18%) vs 76 (35%) were >60 years of age, 86 (15%) vs 32 (15%) were cirrhotic, 70 (12%) vs 40 (18%) were heavy alcohol users (>40 g/day [men]/>30 g/day [women]), 45 (8%) vs 48 (22%) had a history of injecting drug use, and 166 (29%) vs 93 (42%) were on opioid substitution therapy (OST), respectively. The most frequently reported reason for not initiating treatment was patient wish (93, 42%), particularly due to fear of treatment (38, 17%) or adverse events (29, 13%). Additional frequently observed reasons for not initiating treatment included perceived or expected lack of compliance, high patient age, comorbidities, drug/alcohol abuse, and OST (Figure).
Conclusion: In this real-world population, 28% of documented patients with chronic HCV infection did not initiate treatment. Reasons to not initiate treatment other than patient wish included high age, drug abuse, and heavy alcohol abuse. Educating hesitant patients on the importance of treatment and overcoming historic barriers to initiating treatment, such as drug and alcohol use, is needed to achieve HCV elimination.

SAT288

Description of HBV-infected persons presenting late to specialist care in 10 Spanish centres: A retrospective registry review

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Background and Aims: There are an estimated 248 million people living with chronic hepatitis B in the world. Since 2008, there has been a consistent increasing trend in reported chronic HBV cases and continued importation of cases from high endemic countries to many EU countries. Despite Spain having screening and vaccination policies in place and unrestricted access to therapy, people present late to specialist care. We describe the characterists and country of origin of HBV-infected patients in Spain.
Method: We conducted a retrospective cohort study through clinical history revision of patients seeking first time care with a liver specialist in ten tertiary Spanish hospitals between January 2018 and June 2019. Late presentation includes advanced liver disease (ALD) defined by significant fibrosis (≥F3 assessed by either APRIscore >1.5, FIB-4 >3.2, transient elastography (FibroScan) >9.5 kPa or biopsy ≥METAVIR stage F3) with no previous antiviral treatment. Prevalence of ALD at first consultation, country of origin, and risk factors were analyzed.
Results: 398 patients were identified of which 59.8% were male and 54.5% were non-Spanish born. The average age was 46 and the average time from diagnosis to arriving in specialist care was 5.1 years. Patients whose country of origin was Africa made up 19.3% of all HBV cases with 28.5% (22/77) from Senegal followed by Guinea (15; 19.5%) and Ghana (7; 9.1%) (See Fig 1).11% of HBV cases were in Chinese-born individuals (n = 44) and four presented late to care. Non-Spanish born were significantly younger than Spanish born (38 vs 57 years; $p < 0.0001$) and Senegalese and Chinese migrants had a similar average age (34 and 38 years, respectively). Late presentation was detected in 11.6% (n = 46) of all cases and men were more likely than women to present late (6.9% vs 14.7%; $p = 0.006$). Those who presented late were older than those who did not (57 vs 46 years; $p < 0.0001$) and Spanish-born were more likely to present late to care compared to foreign-born individuals (17% vs 7%; $p < 0.0001$).
Conclusion: Late presentation to HBV care is an issue in Spain. Targeted screening programs for high-risk Spanish populations and migrants arriving from high-endemic countries like Senegal and China need to be implemented. More than half of all reported HBV cases were in non-Spanish born persons. If Spain is to meet WHO targets to eliminate viral hepatitis as a major public health threat, efforts need to be made to identify HBV patients sooner.

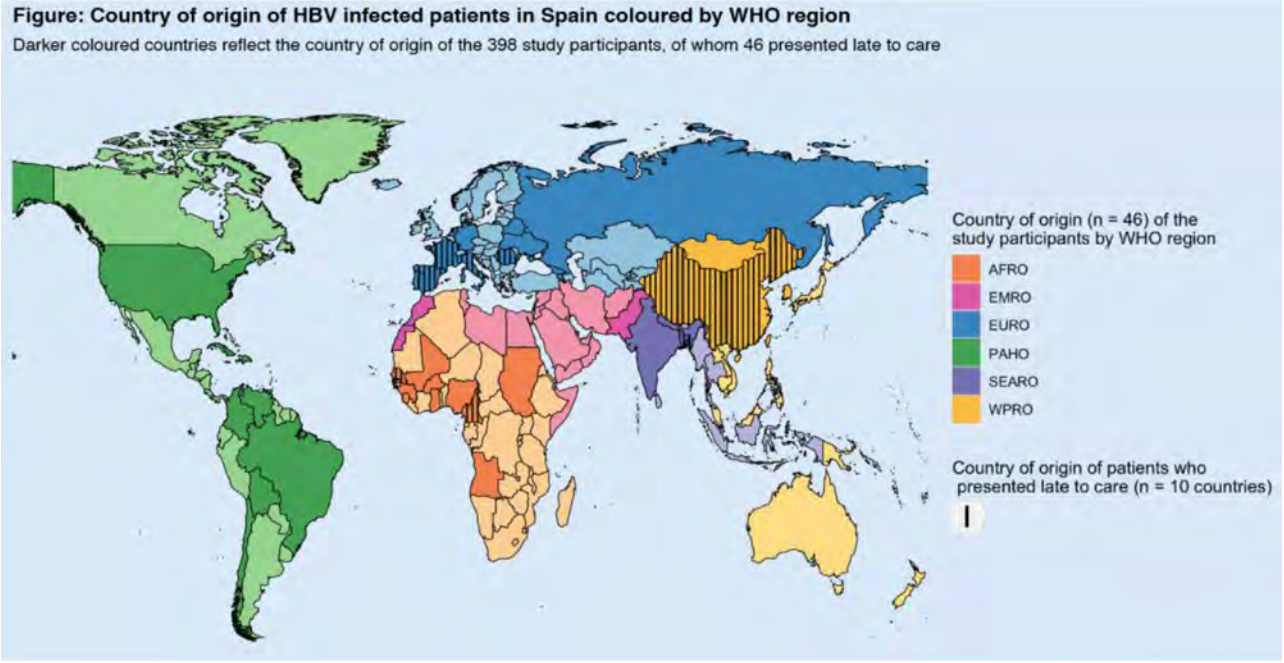

Figure: (abstract: SAT288)

SAT289

The prevalence of hepatitis C amongst people who use performance and image enhancing drugs - a systematic review

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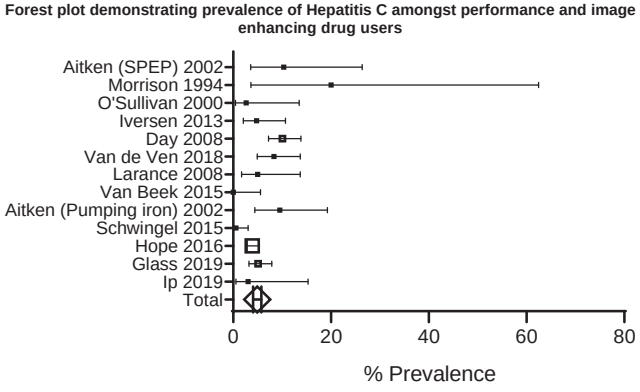
Background and Aims: The injection of performance and image enhancing drugs (PIEDs) is an emerging health concern and the prevalence of Hepatitis C virus (HCV) in this population is poorly understood. To guide the NHS England HCV elimination strategy, the prevalence of HCV within this population needs to be established. We therefore conducted a systematic review to quantify HCV prevalence among people injecting PIEDs.

Method: The systematic review was conducted in accordance with the PRISMA statement. EMBASE, Medline, PsycINFO, CINAHL and Scopus databases were searched. Inclusion criteria were any study reporting HCV prevalence among any population that injected PIEDs. Quality was assessed using an adapted Newcastle-Ottawa Quality Assessment Scale.



Results: Thirteen studies met the inclusion criteria. These included 2491 PIED users in studies from Australia (n = 8), United Kingdom (n = 3), Brazil (n = 1) and United States of America (n = 1). The weighted pooled prevalence was 5.06% (range 0-20%) amongst a demographic that was predominantly male. The Forest plot demonstrates the individual prevalence per study and the pooled prevalence with calculated confidence intervals (for total users, 4.26–5.99%). There was heterogeneity between studies due to inconsistent sampling strategies.

Conclusion: Prevalence rates within the included studies indicate PIED users are a high risk group for HCV. This justifies the need for a public health focus on this population as part of the global elimination strategy. However, study heterogeneity and low quality highlights the need for cross-sectional studies to accurately quantify the scale of the epidemic.

SAT290

Cost-effectiveness of scaling-up treatment with nucleoside analogue (NA) for chronic HBV infection: Towards a simplification of recommendations? (ANRS study)

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Background and Aims: A high rate of viral suppression can be obtained with current NA treatments in chronic HBV infection. Response to treatment highly reduces the risk of progress to cirrhosis

Table: (abstract: SAT290)

	Treated patients																Outcomes			
	HBeAg+Infection				HBeAg+Hepatitis				HBeAg−Infection				HBeAg−Hepatitis							
Strategy	<F2	F2	F3	F4	<F2	F2	F3	F4	<F2	F2	F3	F4	<F2	F2	F3	F4	Life years	QALY	Lifetime costs	ICER €/QALY
S1°	If >30 years			all	If ALT >2 ULN	all			untreated			all	If ALT >2 ULN	all			24.06	19.65	41595	
S2	If >30 years			all	all				untreated			all	all				24.07	19.66	41819	Dominated*
S3	If >30 years	all			If ALT >2 ULN	all			un-treated	all			If ALT >2 ULN	all			24.26	19.85	43872	11385
S4	all				all				all				all				24.32	19.91	45807	32250

°EASL guidelines.
*Weakly dominated strategy: higher ICER than that of a more effective alternative strategy

and its complications; this raises the question of expanding treatment eligibility. The aim of this study was to evaluate the cost-effectiveness of providing treatment to all patients with chronic HBV infection.

Method: A Markov model was developed to simulate disease progression in naïve HBV mono-infected adults, from diagnosis to death. Outcomes were compared for 4 strategies (Table). Patients characteristics were obtained from the French ANRS CO22 HEPATHER cohort. Background and liver disease-related mortality, disease progression rates, viral and biochemical response, and quality adjusted life years (QALYs) inputs were from French and international literature. Direct costs related to health states, including ambulatory and hospital fees, were obtained from French chronic HCV-infected patients. Prices of generic NAs were set at €1333.80 per year. The study perspective was societal. Discount rate was 2.5% for costs and effectiveness. Incremental cost-effectiveness ratios (ICERs) were interpreted according to French GDP per capita (€39,350 in 2017). Extensive sensitivity analysis was performed.

Results: Treating all patients (S4) was the most expensive but also the most effective strategy (with a lifetime mean gain of 0.06, 0.25 and 0.26 QALYs compared to S3, S2 and S1, respectively) and was cost-effective compared to S3 (ICER = 31,682 €/QALY). S2 was dominated by S3 that was highly cost-effective compared to S1 (ICER = 11,572 €/QALY). In sensitivity analysis, parameters having the greatest impact were utilities values under treatment, with or without response: a 10% decrease in health-related utilities for non-responsive patients increased the ICER beyond the French GDP per capita (44,986 €/QALY).

Conclusion: At current NAs efficacy and costs, expanding treatment eligibility to all patients with chronic HBV infections is cost-effective.

SAT291

Hepatitis C continuum of care and predictors of direct acting antiviral treatment among persons who inject drugs in Seattle, Washington, USA

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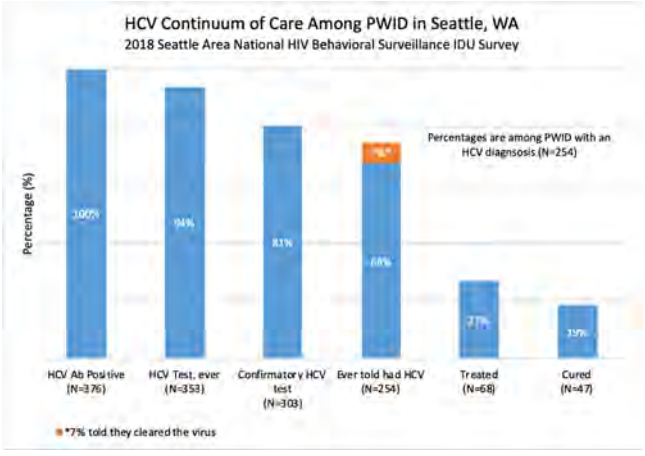
Background and Aims: Direct acting antivirals (DAAs) have revolutionized the landscape of hepatitis C (HCV) care. However, treatment rates among persons who inject drugs (PWID) have historically been low, and it is unclear whether DAA receipt in this population is sufficient to reach elimination goals. We report the continuum of care for HCV and describe predictors of treatment with DAAs among PWID in Seattle, Washington, USA.

Method: This study analyzed data from the 2018 Seattle area National HIV Behavioral Surveillance (NHBS) survey of PWID. Persons were included in the study if they were ≥18 years of age; injected drugs in the past year; and completed the core NHBS survey, a local survey supplement, and rapid HCV antibody test. Among those who were HCV antibody positive, we calculated the proportion who self-reported prior receipt of: 1) any HCV test, 2) a confirmatory HCV test, 3) a diagnosis of HCV, 4) HCV treatment, and 5) HCV cure. Proportions were subsequently stratified by gender and age. Multivariable logistic regression, accounting for the respondent driven sampling method, was used to calculate the adjusted odds ratios (AOR) for having received DAA therapy among those who tested HCV antibody positive.

Results: The sample included 533 PWID, 376 (71%) of whom tested positive for antibodies to HCV. Among those who were HCV antibody positive, 94% reported any prior HCV test, 81% reported a prior confirmatory HCV test, and 68% were previously told they had HCV. Of those reporting a prior diagnosis of HCV, 27% had undergone treatment, with 19% of those diagnosed achieving a cure. Among those diagnosed, fewer women had received HCV treatment (16%) than men (31%), and fewer PWID <40 years of age had been treated (13%) than PWID ≥40 years of age (33%). In a multivariate model, age (AOR 1.04 per year, 1.02–1.05), homelessness (AOR 0.52, 0.31–0.88) and gender were strong predictors of DAA therapy, with women being 58% less likely than men to have received prior treatment with DAAs (AOR 0.42, 0.23–0.75).



Conclusion: Despite high rates of HCV testing among PWID in Seattle, treatment rates remain low in the DAA era. In particular, treatment of women, young adults and persons experiencing homelessness is lagging behind in this high-risk urban cohort. While falling drug costs and the recent removal of DAA prior authorization requirements for Medicaid patients in Washington State may improve treatment uptake in the coming years, increased efforts are needed to link PWID into care, particularly women, young adults and homeless individuals.

SAT292

Dried blood spots are a useful tool for hepatitis A screening in the pandemic areas with medical resource-limited condition

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Background and Aims: Approximately 1.4 million people are infected with hepatitis A virus (HAV) worldwide each year and it caused approximately 11,000 of deaths in 2015 (WHO, 2018) due to its complication. The majority of HAV infection is transmitted fecal-orally via contaminated food and water especially in the areas where water drainage and sewage system are suboptimal. Therefore, HAV infection is closely related to the public health environment. Furthermore, It is difficult to conduct the sero-epidemiological survey by venous blood collection and to grasp anti-HAV prevalence accurately in the medical resource-limited areas. However, Dried Blood Spot (DBS) is a test kit that can collect blood with less invasive and easier than venous blood collection, and measurement of HAV sero-markers using DBS has not been reported so far. In this study, we aimed to establish the method for epidemiological survey of HAV infection using DBS in the developing countries.
Method: This study was conducted in 2017 among 5–7 years old children and their mothers living around Phnom Penh, Cambodia using multi-stage cluster sampling method. The samples were collected using both DBS (HemaSpot-HF blood collection device (HS), 60μl whole-blood/kit) and venipuncture. HS comprises absorbent paper equally separated into eight fragments with desiccant and is covered by a clear rubber with a hole in the centre. Three fin of absorbent paper were mixed and stirred with lysis buffer in 2 ml tube to get supernatant fluid. Then, a mixture of 20μl of supernatant fluid and 60μl of 5% albumin was measured for total anti-HAV (CLEIA) using Vitros Immunodiagnostic Product (Ortho Clinical Diagnostics). Cut off index (COI), sensitivity and specificity for anti-HAV measurement from HS sample were calculated by Receiver Operating Characteristic curve (ROC) analysis.
Results: DBS and serum samples were collected from 517 children aged 5–7 years and their 405 mothers. Anti-HAV positive rate by serum samples was 41.0% {positive: 212/517, borderline: 3/517, negative: 302/517} in children and 99.8% {positive: 404/405, border line: 0/405, negative: 1/405} in mother. By ROC analysis, C.O.I, the sensitivity and specificity of DBS samples (N = 922) were 2.1, 94.8% and 99.0% respectively.
Conclusion: The method for epidemiological survey of HAV infection using DBS was succeeded to be established.

SAT293

Viral hepatitis in Belgian prisons: a first-time multicenter prevalence study

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Background and Aims: Prevalence of hepatitis C virus (HCV) and hepatitis B virus (HBV) infection among prisoners is many times higher than in the general population. The high rates of viral hepatitis infection in prisoners, and the substantial risks associated with an untreated infection underline the need for screening and access to treatment in prisons. To date, there is no targeted screening in Belgian prisons and currently there are no data on the prevalence of HCV or HBV infections in prison. Through targeted screening, we want to map the prevalence of HCV and HBV in prisons in Belgium.
Method: The study started on 1 April 2019 in several prisons for both prisoners in pre-trial detention and long-term convicts throughout Belgium. The eligible candidates (>18 y and signed informed consent form) were tested by finger prick for HCV antibodies (Ab) using the Oraquick® test and hepatitis B surface antigen (HBsAg) using the HBsAg Rapid Test Device®. While waiting for the results (20 minutes), an encoded questionnaire was filled out.
Results: From 1 April 2019 till 7 November 2019 a total of 456 prisoners were screened. Of these, 21 (4.6%) tested positive for HCV Ab and 5 (1.1%) tested positive for HBsAg. The prevalence of HCV Ab did not differ in prisoners in pre-trial detention compared to long-convicts, respectively 10/160 (6.3%) and 11/285 (3.9%, p = 0.159). All participants who tested positive on one of the tests was referred to the physician in prison for a vene puncture to determine HCV RNA. To date, HCV RNA was determined in 12/21 and was present in 8 (66.7%).
Conclusion: These preliminary results show an increased prevalence for HCV Ab in prisons in Belgium. This is markedly lower than mentioned in previous European studies.

SAT294

Limburg is the first Belgian province on track for hepatitis C virus eradication in the most important group at risk: People who use drugs

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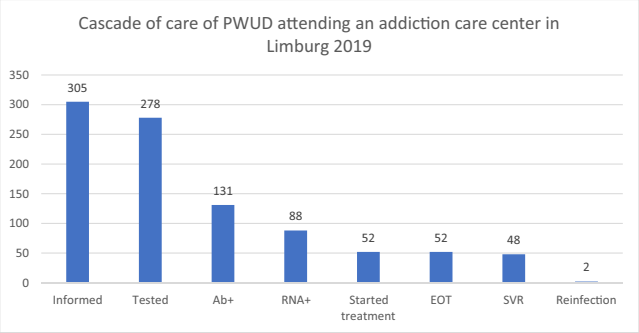
Background and Aims: Hepatitis C virus (HCV) is one of the leading causes of chronic liver disease and liver-related deaths worldwide. HCV and HCV reinfection is most prevalent in Belgian people who inject drugs (PWID). PWID are at the heart of the ongoing HCV epidemic. To avert future liver disease and new infections, prevention of HCV transmission among PWID is crucial. Recent modelling shows that to eliminate HCV in Belgium, more people must be tested and linked to care, and the average percentage of patients to be treated per year out of the total pool of patients to be treated needs to be fixed at a minimum of 8% of the current patient pool. The aim of this project is to eradicate HCV in people who use drugs (PWUD) in an addiction care centre in Limburg and to monitor reinfection after therapy.
Method: In this ongoing prospective cohort study started in November 2016 in an addiction care centre, case management is performed by an HCV nurse. The nurse informs PWUD about HCV, and performs on-site screening of HCV anti-bodies (Ab) using the OraQuick® rapid test by finger prick or HCV RNA by vene puncture upon informed consent. All HCV RNA positive PWUD are referred to

the hospital for potential treatment. The HCV nurse accompanies them if necessary. After cure, these PWUD are monitored by the HCV nurse for potential reinfection by yearly screening.
Results: In Limburg 357 clients received opiate agonist therapy in 2019. The case manager personally informed 305/357 (85.4%). Out of 305 informed clients 278 (91.1%) accepted on-site screening. Of those who were chronically infected, 52/88 (59.1%) started therapy. All 52 (100%) PWUD were cured successfully. From the start of the project to the present only two out of 52 (3.8%) treated PWUD got reinfected due to ongoing intravenous drug use.



Conclusion: Limburg is as the first Belgian province on track to meet the goals of the World Health Organization to eradicate HCV by 2030 in a PWUD population. With the case management program every PWUD attending an addiction care center in Limburg can be screened and after treatment they are closely monitored for reinfection.

SAT295

Early treatment of hepatitis C virus improves health outcomes and yields cost-savings: A modeling study in Argentina

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Background and Aims: Patients with hepatitis C virus (HCV) face increased healthcare costs due to hepatic and extrahepatic complications. The new all-oral direct-acting antivirals have dramatically improved the sustained virological response (SVR) rates. Achieving SVR has shown to increase health benefits and reduce medical costs. While treatment in early stages of liver fibrosis has been shown to reduce liver-related complications and lower healthcare costs compared to treatment in later disease stages, it is often delayed and patients in early fibrosis stages have limited access to effective treatment. Thus, this study evaluated the clinical and economic impact of treating patients in Argentina with HCV at early vs late stages of liver disease.
Method: A Markov model of the natural history of HCV was used to forecast liver-related and economic outcomes over a lifetime from the perspective of Argentina's social security sector. Health utilities and transition probabilities were drawn from published literature. Treatment attributes and patient demographics were based on registrational clinical trials of glecaprevir/pibrentasvir. Costs were based on tariffs from Argentina's social security system. Analyses were conducted for patients with HCV genotypes 1–6 and different fibrosis stages of liver disease: mild (F0-F1); moderate (F2-F3), and compensated cirrhosis (F4). Health outcomes included lifetime risks of compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), liver transplant (LT), and liver-related death (LrD). Other outcomes included lifetime costs and quality-adjusted life years (QALYs), both discounted at a 5% rate.
Results: In this simulated model, treating HCV infection at early stages of fibrosis appeared to reduce the risk of CC, DCC, HCC, LT and LrD (Table). Delaying treatment increased long-term total lifetime costs and provided fewer QALYs. Early treatment was a dominant strategy regardless of time of delay as it delivered more QALYs at lower costs.

Outcome	Liver fibrosis stages		
	Mild (F0-F1)	Moderate (F2-F3)	CC (F4)
CC Risk (%)	7.2	17.6	100.0
DCC Risk (%)	2.0	6.1	8.3
HCC Risk (%)	0.9	2.6	27.7
LT Risk (%)	0.2	0.6	1.9
LrD Risk (%)	1.8	5.8	30.7
SVR (%)	97.9	97.9	98.9
Total Costs (AR$)	954,018	967,673	1,437,816
Total QALYs	11.5	9.9	7.5

Conclusion: This analysis suggests that treating HCV at early stages improves health outcomes and reduces the total cost in Argentina. Hence, clinical and policy decision-makers should avoid delays and restrictions in HCV treatment.

SAT296

Tailored message interventions promote the number of participants in viral hepatitis screening for Japanese workers - multicenter trial of 1,127,596 general checkup applicants

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Background and Aims: Although more than 20 million community residents have been provided an opportunity to undergo hepatitis B virus (HBV) and hepatitis C virus (HCV) screening by the Japanese government, actions against hepatitis at work sites in Japan have not yet been fully implemented. In Japan Health Insurance Association, which is belonged to about 40 million Japanese who are working in Medium and Small Sized Companies, the attendance rates of hepatitis screening were low prevalence even the cost of only € 5. The aim of this study was to investigate the effectiveness of a tailored message intervention promoted the numbers of viral hepatitis screening, compared with a typical message.
Method: A leaflet which was a tailored message condition for the screening was individually sent to more than one million Japanese workers at 3 brunches of Japan Health Insurance Association who wish to get annual general checkup in 2018 as multicenter trial. For control subjects, we enrolled general checkup applicants with a a typical message condition in 2017. The main outcome measure was attendance rates in HBV and HCV screening which were examined HBs antigen (HBsAg) and Anti-HCV antibody (anti-HCV), respectively.
Results: There was a significant difference in viral hepatitis screening attendance rates between the tailored matched-message condition (n = 112,581 10%) and the control (n = 13,452 1.3%; $p < 0.001$). One thousands thirty workers (1.2%) were positive of HBsAg (n = 588, 0.52%) and anti-HCV (n = 442, 0.39%), respectively. Among them, four hundred ninety-four (48%) were confirmed to visit specialists within 6 months after the screening. One hundred fourteen in HCV positive

	The number of General Checkup		The number of screening (rate)		The number of positive (rate)	
Branch	Control	Tailored Message	Control	Tailored Message	HBsAg	Anti-HCV
A	376,223	404,838	4,791	72,508	413	227
B	213,396	256,650	2,365	20,292	96	54
C	418,649	466,108	6,296	19,781	79	161
Total	1,008,268	1,127,596	13452(1.3%)	112581(10%)	588(0.52%)	442(0.39%)

Figure: (abstract: SAT296)

(26%) were treated with IFN-free direct-acting antivirals and five males in their 50–60 s (0.4%) were detected hepatocellular carcinoma.

Conclusion: There are still many patients who infected HBV and HCV at work sites in Japan. A tailored-message intervention designed to increase the viral hepatitis screening rates in the Medium or Small Sized Companies. Promoting hepatitis virus screening for workers at general check-up can help detect carriers who are unaware of their infection and require to therapy for viral elimination and cancer.

SAT297

Data from a large, public sector hepatitis C program in Punjab, India

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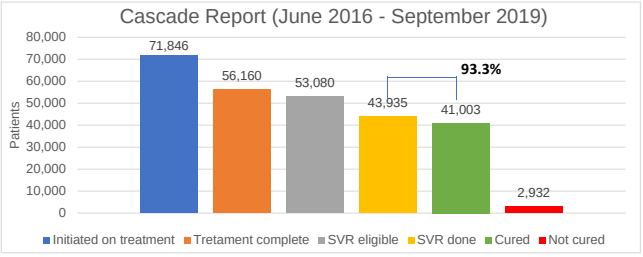
Background and Aims: Hepatitis C virus (HCV) is a rising challenge in India, with an estimated 5.2–13 million people anti-HCV antibody positive. The state of Punjab has a higher prevalence of HCV compared to national prevalence estimates (3.3% vs. 0.5–1.5%). In 2016, the Punjab government launched the 'Mukh Mantri Punjab Hepatitis-C Relief Fund' to provide free HCV treatment to all infected residents. The Clinton Health Access Initiative, in collaboration with the Punjab government, developed an online Monitoring & Evaluation (M&E) system, the first in the country for HCV, to measure outcomes of program implementation, identify gaps and areas for improvement, and ultimately optimize effectiveness of the program. This analysis documents the results achieved to date in Punjab's HCV program based on M&E system data.

Method: Data from 25 medical facilities was downloaded using the M&E system in Punjab. Descriptive statistics were utilized to assess the demographics and clinical characteristics of the patient population and the percentage of patients achieving cure as determined by the sustained virological response 12 weeks (SVR12) following treatment.

Results: From June 2016-September 2019, 71,846 patients were initiated on direct acting antiviral (DAA) therapy for HCV in Punjab. 60.1% of patients were 31–60 years and 66.4% of patients were male. 86.2% of patients were non-cirrhotic. Unsafe injection use and intravenous drug use were the most common risk factors reported by patients (32.0%). The most common drug regimen prescribed was SOF/DCV for 12 weeks (81.1%). Since initiation, 56,160 patients have completed treatment (78.2% of those who initiated treatment), 5,643 patients are currently on treatment, and 10,043 (14.0%) were lost to follow-up after treatment initiation. SVR12 was conducted for 43,935 patients (78.2% of those who completed treatment), of which 41,003 (93.3%) demonstrated cure.



Conclusion: Punjab successfully underwent a massive scale-up of HCV treatment in the public sector. Although loss to follow-up was significant, among those who returned for follow-up, SVR12 was high. Generic SOF/DCV performed very well across a variety of genotypes in this real-world setting. Future areas of research should focus on improving retention and addressing the small but significant problem of virologic failure with first line DAAs.

SAT298

Implementation of electronic monitoring and evaluation system for hepatitis C in Punjab, India

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Background and Aims: Hepatitis C virus (HCV) is a rising challenge in India, especially in the northern state of Punjab where the prevalence is estimated to be 3.3%. Nowadays, information plays a key role in disease prevention planning and decision-making processes. Thus, the Clinton Health Access Initiative (CHAI), in collaboration with Punjab government, developed an online Monitoring and Evaluation (M&E) system for the state to record the patient information and create meaningful interventions. This abstract documents the implementation process of the first ever electronic HCV M&E system in Punjab.

Method: CHAI designed treatment cards and a corresponding electronic M&E system to capture relevant patient information. The system is comprised of eight patient modules across the cascade of care: Registration, screening, viral load testing, base-line liver and blood testing, co-infection history, drug prescription, dispensation schedule and Sustained Virologic Response testing (SVR). A combination of open source technologies (PHP & MySQL) and an android application were utilized to capture patients' data offline, as some health facilities did not have stable internet connection. The data from the application can be stored offline and later synced online once internet connection is established. A web-based reporting dashboard was also developed to enable program managers to monitor program outcomes and take timely corrective action as

needed. Reports on the patient cascade and missed appointments were designed to identify trends in loss to follow-up at different stages and identify areas/facilities/patients needing additional support. To roll out the system efficiently, CHAI conducted comprehensive trainings for healthcare workers and partners which included hands-on practice, and assisted with additional on-site trainings as needed.

Results: As of today, the system has been successfully implemented in 25 medical facilities (22 district hospitals and 3 government colleges) in Punjab and captured data from ~100,000 patients screened for HCV. Results show that an electronic M&E system for the management of hepatitis was a requirement in Punjab because the infrastructure provided useful information to all the stakeholders. This system has enabled the government and key stakeholders to maintain accurate patient records, monitor results, and follow-up efficiently. Follow-up actions taken based on information provided by the M&E system have led to program improvements around diagnostic algorithms, treatment, and patient retention in care.

Conclusion: Overall, Punjab's M&E system has generated meaningful information that has been utilized to design targeted interventions for high risk groups and strategies for screening scale-up. In 2019, the system was used as a blueprint for India's national HCV M&E system to track program scale-up and mitigate challenges along the way.

SAT299

Hepatitis C elimination in hemodialysis population of a county - an innovative collaborative care model in Taiwan

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Background and Aims: HCV micro-elimination, which focuses on smaller, targeted high-risk subpopulations, has been proposed for achieving global elimination of HCV. Patients with end stage renal disease (ESRD) had a high incidence of HCV infection (8–12%). There are several barriers to treat HCV patients in dialysis centers due to unawareness, unwillingness, and difficulty of referral due to long journey and patients' disability. The objective of this study is to demonstrate the efficiency of the novel delivery model in achieving

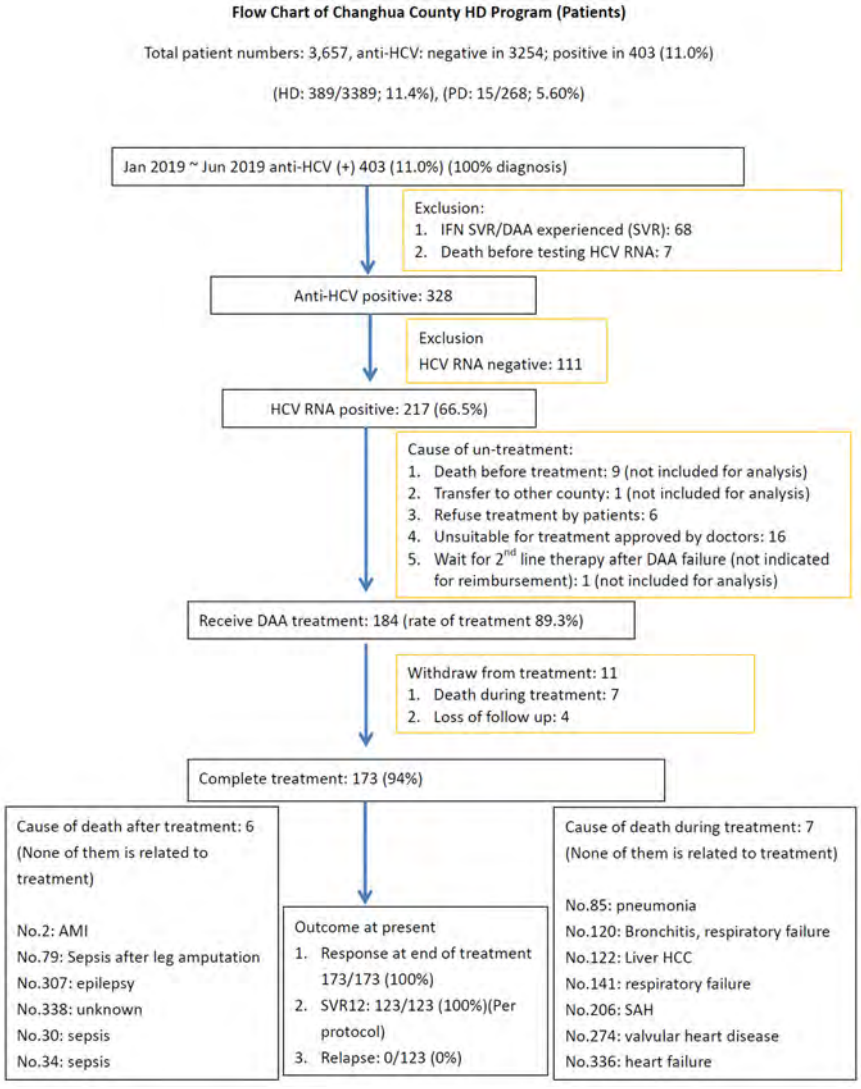

Figure: (abstract: SAT299)

the elimination of HCV among hemodialysis patients in 31 dialysis centers in the jurisdiction area under a Public Health Bureau of Changhua County in Taiwan.
Method: A total of 31 hemodialysis (HD) centers are managed and the micro-elimination program was implemented (led by the public authority). To overcome the barrier of HCV treatment, mobile clinics were set up at HD centers that did not have a hepatologist/gastroenterologist. This team was responsible for delivering a continuum of care from screening, diagnosis, treatment, and follow-up on site. The treatment regimen included either grazoprevir/elbasvir (GZP/EBV; Merck) or glecaprevir/pibrentasvir (GLE/PIB; AbbVie). The primary outcome includes the achievement of HCV micro-elimination, which was defined as per WHO criteria and sustained virological response rates at 12 weeks after treatment (SVR12).
Results: A total of 3,657 patients visiting Changhua County HD and peritoneal dialysis (PD) centers from Jan 2019 to Jun 2019 were screened. Among the patients, 403 (11.0%) patients were seropositive for HCV. Finally, a total of 184 viremic patients received treatment (coverage rate 89.3%). The flow chart of diagnosis and treatment is shown figure. The mean age is 66 years, ranged from 40 to 90 years old, and the longest dialysis period is 30 years. Genotype (GT)-1 patients made up 50%, and GT-2 made up about 40% of patients. Finally, 83% of patients were treated with the GLE/PIB, the others were GZP/EBV and LDV/SOF. Among the treated patients, 173 patients (94%) completed the course of treatment. Seven patients died during treatment, and 6 patients died after EOT and before SVR12. None of the death was considered to be related to DAA therapies. The response rate at EOT and SVR12 are all 100% according to per protocol analysis. Notably, we also surveyed the incidence of HCV for the 619 staff at HD centers with a coverage rate of 98.7%. Only 5 patients were positive for anti-HCV (0.82%) in which 4 patients have been already treated. Only 1 patient was viremic but has since completed DAA therapy under this program.
Conclusion: Our study has demonstrated that the novel treatment-delivery approach with mobile clinics can achieve elimination of HCV in ESRD subpopulation in a very short period of time. We hope that the success of this program would encourage the implementation of methods to accelerate HCV eradication globally.

SAT300

Unusual occurrence of hepatitis B infection in Upper Egypt

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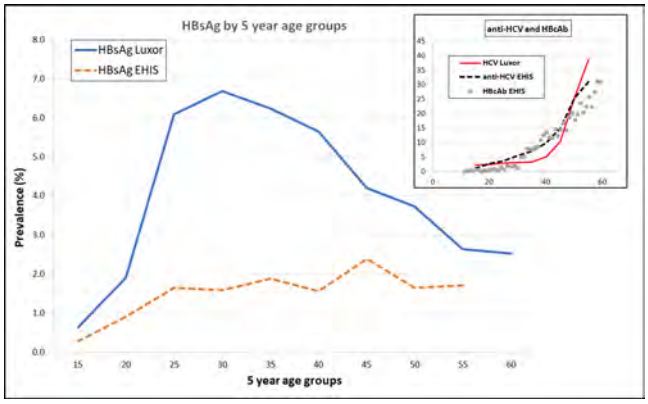
Background and Aims: The high prevalence of HCV in Egypt is well documented. The Egyptian government has implemented a countrywide program to control HCV, which includes mass screening campaigns to diagnose and treat asymptomatic cases at a national level. Much less is known on the prevalence of HBV in Egypt.
Method: Luxor HCV Treatment Center was established in 2016 by the national Tahya Misr Fund to screen and treat HCV infection in Luxor city and the surrounding areas in Upper Egypt. The center adopted a unique mass screening program for both HBV and HCV. Participants aged 16 years and older were screened, at no cost, for anti-HCV antibodies (anti-HCV) and hepatitis B surface antigen (HBsAg) using third generation enzyme immunoassays (Enzygnost® Anti-HCV and HBsAg). This report focuses on HBV screening results in Luxor with comparison to the national level HBV results of the 2015 Egyptian Health Issues Survey (EHIS).
Results: From June 2016 to May 2017, 67,007 persons were screened for HBsAg at Luxor center, including 31,945 males (47.7%) and 35,062 females (52.3%). The mean age was 43.6 years. There were 2,947 persons (4.4%) positive for HBsAg. HBsAg prevalence was significantly higher in males versus females (6.2% vs. 2.75% OR = 2.3; $p < 0.0001$). The age specific pattern of HBsAg prevalence has a steep increase to age 31 (7.7%) followed by a decline to age 60. In EHIS 2015, 26,047 persons aged 1-59 years were screened for anti-HCV, Hepatitis B core antibody (HBcAb) and HBsAg, including 12,319 males (47.3%) and 13,728 females (52.7%). The overall prevalence of HBcAb was 9.9% (11.3% in males - 8.7% in females), compared to 1% for HBsAg (1.2% in males - 0.8% in females). This included 274 persons sampled from the Luxor area, in which HBcAb and HBsAg prevalence was 18% and 1.7% respectively. The age specific patterns of anti-HCV, HBcAb and HBsAg in EHIS and Luxor study are compared in Figure (1). Age specific HBsAg is higher in Luxor than the national estimates. Age specific HBcAb is strongly associated with anti-HCV in both the Luxor and EHIS estimates.



Conclusion: HBV infection is very high in Egypt as indicated by the high prevalence of HBcAb (9.9%) reported in EHIS. Most of these infections spontaneously resolve (HBcAb positive), and 1% of the patients remain chronically infected (HBsAg positive). Our results from Luxor showed an epidemiologically significant higher HBsAg prevalence (4.4%), which is higher in males and among those in middle age. This is a source of ongoing HBV transmission in the community. HBV screening and vaccination should be strengthened in this area of Upper Egypt.

SAT301

A novel test and treat hepatitis C micro-elimination project among underserved communities in Islamabad, Pakistan

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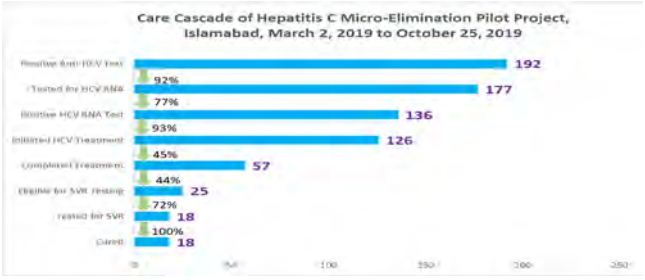
Background and Aims: Pakistan has a large burden of hepatitis C virus (HCV) infection, and access to care and treatment is limited. In order to increase access for underserved populations, a same-day testing and treatment initiation model program for adults in marginalized communities (i.e *slums*) in Islamabad was launched on March 02, 2019. We describe the early results of the program.
Method: A total of 17 slums with an estimated total population of 50,000 in Islamabad have been selected by the Ministry of National Health Services, Regulations and Coordination for the project. This project includes free of charge hepatitis C testing and treatment and utilizes trained community health workers (CHWs). The CHWs visit every dwelling in the slum and offer household members aged ≥18 years screening for hepatitis C by a rapid hepatitis C antibody (anti-HCV) test. Those that test positive are referred to an established clinic

for diagnosis of active HCV infection (RNA) by GeneXpert. RNA results are made available to patients within two hours. If found to be infected with HCV, additional blood is obtained and tested to calculate the AST to Platelet Ratio Index (APRI). Subjects then receive counseling, and their first 4-week supply of sofosbuvir plus daclatasvir and the first of three doses of hepatitis B vaccine during the initial clinic visit. A treatment regimen of 12 weeks for non-cirrhotic (APRI<1.5) patients is prescribed and given by the medical officer of the project. Patients with an APRI ≥1.5 are treated by a staff hepatologist. Patients are seen every 4 weeks at the clinic and given refills on their medications and queried about adverse reactions, until the end of treatment. RNA testing is conducted at 12 weeks following completion of treatment to determine cure i.e. sustained virologic response (SVR). The CHWs ensure referral and follow-up of HCV infected persons.

Results: As of October, 25 2019, a total of 5,209 participants have been screened from three *slums*, 192 (3.6%) tested positive for anti-HCV and were referred to receive testing for active infection. Of those, 177 (92%) were tested for RNA, of which 136 (77%) had active HCV infection. A total of 126 individuals (93%) had initiated treatment, of which 57 (45%) had completed treatment. To date, 18 of 25 eligible persons were assessed for SVR and all of them achieved SVR. None of the 126 individuals who initiated treatment had been previously tested or treated for hepatitis C.



Conclusion: Same day hepatitis C testing and treatment initiation is feasible among underserved communities in urban slums in Pakistan. CHWs can be effective in reaching "*hard-to-reach*" populations with limited access to health services and achieving high rates of linkage to care and adherence with treatment for hepatitis C.

SAT302

Classifying people living with hepatitis C virus using a population-level latent class analysis to inform optimal integration of health services

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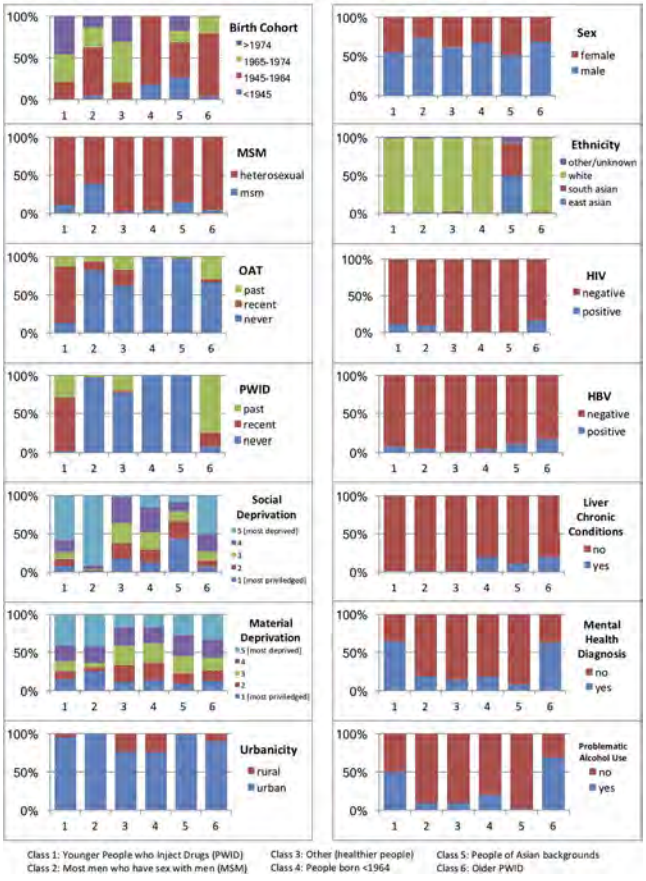
Background: Since the advent of direct acting antivirals (DAAs), hepatitis C virus (HCV) treatment uptake has dramatically increased. As of 2018, only 54.4% of those diagnosed HCV RNA positive have been treated. HCV affects diverse and often overlapping populations, such as people who inject drugs (PWID), men who have sex with men (MSM), and immigrants from endemic regions. Assessing patterns of shared sociodemographic and clinical characteristics among subpopulations using Latent Class Analysis (LCA) may allow for targeted HCV program planning and services.

Method: The BC Hepatitis Testers Cohort includes all HCV cases in BC from 1990 to 2015 followed up to 2018 and linked with data on medical visits, hospitalizations, cancers, prescription drugs, and deaths. LCA was used to group 73,665 people diagnosed with HCV according to shared characteristics previously shown to be related to HCV treatment uptake (age, gender, ethnicity, sexual identity, urbanicity, socioeconomic status, use of injection drugs or opioid agonist therapy, alcohol use, mental illness, co-infections, and liver disease). Models were fit using 1–10 classes, with the best fitting model chosen based on fit statistics, epidemiological meaningfulness, and maximisation of posterior probability for class assignment. Classes were named by defining characteristics.

Figure 1: Characteristics of Latent Classes [on x-axis] of People Living with Hepatitis C in British Columbia.



Results: The best fitting LCA model had 6 classes with the following characteristics: 1. *Younger PWID:* (n = 11,123), included 46% born>1974, 69% recent PWID, 24.0% treated, top prescriber (TP) = general practitioners–36.4%; 2. *Most MSM* (n = 9,751) including 39% MSM, 100% urban, 92% most socially-deprived, 27.7% treated, TP = gastroenterologists (GAS)–32.7%; 3. *Other—healthier people* (n = 8,285): 24% rural, 0% liver disease, 22.1% treated; TP = GAS–35.6%; 4. *People born <1964* (n = 24,244) including 95% born <1964, 19% liver disease, 32.7% treated, TP = GAS–44.1%; 5. *People of Asian backgrounds* (n = 4,744) including 27% born <1945, 92% East/South Asian, 34.2% treated, TP = GAS–61.9%; and 6. *Older PWID* (n = 15,518) including 76% born 1945–1964, 16% HIV+, 76% past PWID, 21.0% treated; TP = infectious disease (ID)–29.3%. The treatment uptake and provider type differed by the LCA class; treatment uptake was lower among PWID and they were mainly prescribed treatment by general practitioner or ID specialists while GAS was the main prescriber for other groups.

Conclusion: LCA identified 6 classes with distinct characteristics which could be utilized to align services. Observed differences in HCV treatment between the classes suggests that the co-occurrence of multiple factors may influence uptake likelihood. Further analysis of health service utilization patterns related to patient profiles may inform optimal layout of services. This analysis may also inform approaches to address systemic barriers that impede care-cascade engagement.

SAT303

Comparison of risk factors for cirrhosis and hepatocellular carcinoma: a large prospective study of UK women

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Background and Aims: Alcohol, smoking, adiposity and diabetes are associated with increased risk of cirrhosis and of hepatocellular carcinoma (HCC), but it is unclear whether the magnitude of the associated risks differ. This study aims to compare the magnitude of these risk factors for cirrhosis and HCC in a large cohort of UK women.
Method: In 1996–2001, a UK prospective study recruited 844,715 women, mean age 57 years (SD 5), with no prior liver disease or cancer who reported drinking at least one alcoholic drink per week. Participants completed a questionnaire at recruitment and were followed by record linkage to routinely collected National Health Service databases on hospital admissions, cancer registrations and deaths for first record of cirrhosis or hepatocellular carcinoma (HCC). Cox regression yielded adjusted relative risks (RRs) for both conditions in relation to alcohol, smoking, body mass index (BMI) and diabetes at recruitment.
Results: During a mean follow up of 18 years (SD 3), 5,999 incident cirrhosis and 1,603 HCC cases were identified. For all the four risk factors, the magnitudes of the associated relative risks were greater for cirrhosis than for HCC, particularly alcohol consumption and current smoking. The respective relative risks were: for ≥15 drinks of alcohol/week vs 1–2 drinks/week, 4.76 (95% CI 4.38–5.18) and 1.21 (95% CI 1.00–1.47); for current vs never smoking, 3.08 (95% CI 2.88–3.28) and 1.81 (95%CI 1.59–2.07); for each 5 unit increase in BMI, 1.40 (95% CI 1.34–1.45) and 1.31 (95% CI 1.21–1.41); and for a history of diabetes vs no history of diabetes, 3.10 (95%CI 2.77–3.47) and 2.26 (95%CI 1.78–2.87). All differences were statistically significant, except for BMI.
Conclusion: The magnitude of the relative risks associated with alcohol consumption, smoking, and to a lesser extent, diabetes and adiposity, were generally greater for cirrhosis than for HCC.

SAT304

Hepatitis C virus testing and treatment in children: results from a global paediatric policy review

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Background and Aims: The first World Health Organization (WHO) global health sector strategy on viral hepatitis calls for the elimination of hepatitis B and C viruses (HBV and HCV) as a major public health threat by 2030. Our aim was to describe current status of hepatitis C policies in WHO Member States with a particular focus on paediatric diagnosis and treatment.
Method: Information on paediatric hepatitis C policies was extracted from current national strategic plans and clinical guidelines available online or through WHO's repository of viral hepatitis national policies, between January and June 2019. Policies on paediatric testing and treatment were summarised and coded.
Results: National policies for hepatitis C were available for 118 of the 194 WHO Member States. Of these 118, most had no policy recommendation for paediatric HCV (n = 77, 65%). HCV testing for children born to mothers with HCV was covered in only 34 (29%) national policies; earliest age at which testing was recommended varied. National policies in only 25 countries (21%) specifically mentioned HCV treatment for children (with a further 20 policies specifying a general "treat all" policy). Countries with recommendations on both testing and treating children (n = 18) were mostly from the European (n = 10), Americas (n = 3) and Eastern Mediterranean (n = 3) regions (Figure 1). Countries with policies only on testing (n = 16) were more geographically diverse but mostly high-income (n = 9) or upper-middle income (n = 3). Seven countries had policies on treatment only and most were high- or upper-middle income (n = 6). At the time of review, 25 country policies included details of paediatric treatment: 8 recommended Direct Acting Antiviral (DAA)-based regimens for adolescents > = 12 years (all published 2017–2019) and the rest recommended interferon/ribavirin-based regimens.

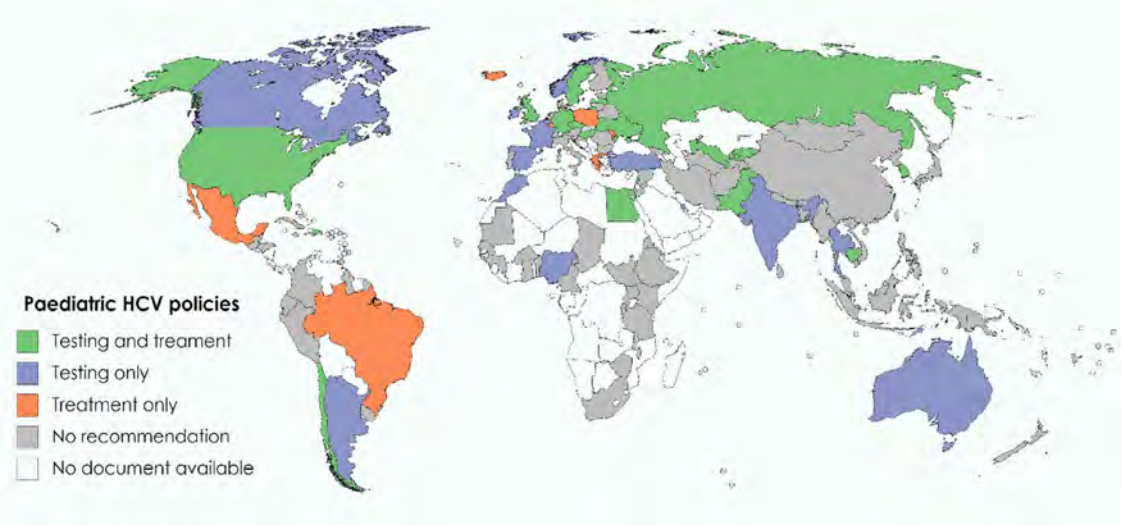

Figure: (abstract: SAT304): Countries with recommendations for paediatric HCV testing and treatment in national policy documents.

Conclusion: While countries have made progress in developing national strategies for elimination of HCV, this review highlights a gap in paediatric HCV policies. As Member States align their national programs with the ambitious WHO targets, children and adolescents must not be forgotten.

SAT305

HCV screening strategies targeting prisoners and immigrants from endemic countries: are they cost-effective?

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Background and Aims: The World Health Organization target for HCV elimination by 2030 has broadened the boundaries of the debate around HCV to strategic and economic considerations. Understanding how to prioritize screening to reach the infected undiagnosed populations is crucial. This is imperative in the UK, where nearly half of the people infected are undiagnosed. This study evaluated the cost-effectiveness of a range of strategies for diagnosing HCV in specific high-risk populations in Scotland (UK) as a case study.
Method: Two high risk populations were identified: prisoners and high prevalence ethnic minorities. A cost-effectiveness analysis was undertaken for each population considering novel screening strategies such as opt-out testing policies in prisons and community outreach activities offering dry blood spot testing compared against the standard care diagnostic pathways for the specific subpopulations. The data sources were anonymised prison testing data and a previously published pilot study on a local outreach testing initiative. A decision tree explored the incremental cost per additional positive patient detected, and a Markov model was employed to present incremental cost per Quality Adjusted Life Years (QALYs) gained and Net Monetary Benefit (NMB) over a lifetime horizon.
Results: Screening prisoners for HCV with opt-out testing resulted in a 7.82-fold increase in detecting positive individuals compared to screening based on symptomatic detection, costing £366 per any additional detected individual. Offering tests at community outreach locations with individuals from countries of increased prevalence costs approximately £2100 per additional detected patient. In the lifetime analysis, both the strategies are highly cost-effective considering a £20,000/QALY threshold, with an incremental cost effectiveness ratio of £1,195 per QALY for the prison population and £4275/QALY for the ethnic-minority community outreach program.
Conclusion: Targeting high risks populations with screening established in prisons and at community outreach locations for ethnic minorities from endemic countries are both highly cost-effective strategies for reaching undiagnosed HCV patients. A combination of these strategies with others targeting high-risk populations such as injecting drug users would be vital to eradicate HCV by 2030.

SAT306

Relationship between metabolic syndrome and ALT level with normal range in the general population

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Background and Aims: This study aimed to investigate the risk of metabolic syndrome in subjects with normal ALT level for the general population.
Method: Between 2007–2015, nationally representative samples from the Korean National Health and Nutrition Examination Survey was used to conduct a cross-sectional study. A total of 43,402 adults (men: 17,535 and women: 25,867) with ALT ≤40 U/L and without a history of hepatitis B, hepatitis C, liver cirrhosis, or liver cancer were analyzed. Stratification of the ALT level (men: <15 U/L, 15~30 U/L, and 30~40 U/L/women: <10 U/L, 10~20 U/L, 20~40 U/L) was done to evaluate for the risk of metabolic syndrome. Metabolic syndrome was defined by the updated National Cholesterol Education Program Adult Treatment Panel III standards.
Results: The prevalence of metabolic syndrome is significantly increased as ALT increases regardless of sex. The proportion of metabolic syndrome in men is 12.6%, 25.2%, and 39.7% in ALT <15 U/L, 15~30 U/L, and 30~40 U/L, respectively ($p < 0.001$) and that of metabolic syndrome in women is 7.2%, 23.3%, and 44.7% in ALT <10 U/L, 10~20 U/L, and 20~40 U/L, respectively ($p < 0.001$). There is an ALT-dependent relationship in the risk of metabolic syndrome within normal ALT level adjusting for age, alcohol intake, and body mass index. The adjusted odds ratios (ORs) of metabolic syndrome in men are 1.55 (95% confidence interval [CI]: 1.38–1.74), and 2.48 (95% CI: 2.16–2.85) in ALT 15~30 U/L, and 30~40 U/L, respectively ($p < 0.001$). And, the adjusted ORs of metabolic syndrome in women are 1.58 (95% CI: 1.35–1.86), and 2.67 (95% CI: 2.26–3.15) in ALT 10~20 U/L, and 20~40 U/L, respectively ($p < 0.001$).

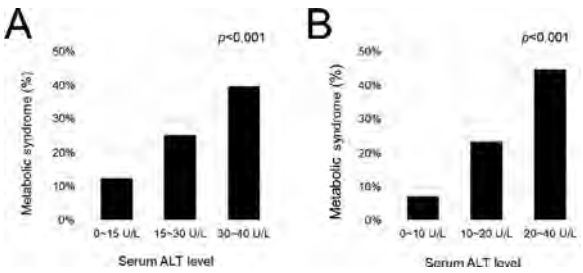

Figure: The prevalence of metabolic syndrome in subjects with ALT ≤40: male (A) and female (B). Abbreviations: ALT, alanine aminotransferase.

Conclusion: Although within the normal range, there is a greater risk of metabolic syndrome as ALT levels increase. ALT levels may potentially be a useful marker in detecting metabolic syndrome in the general population.

SAT307

Are UK NAFLD/NASH referral pathways ready to tackle the emerging epidemic? A rapid systematic public health evidence synthesis

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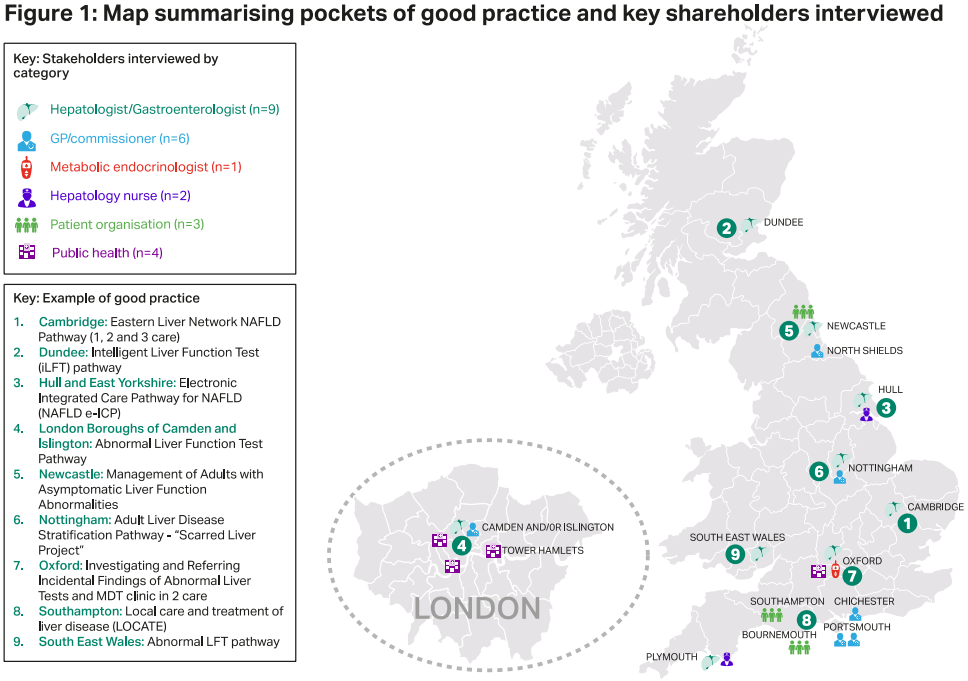
Background and Aims: Non-alcoholic fatty liver disease (NAFLD/NASH) is an emerging and under-recognised global public health problem, primarily being driven by the "Diabesity" epidemic (obesity and type 2 diabetes). Real-world prevalence of NAFLD is unknown but synthetic UK estimates suggest ~20–30% (>13 million) adults. The majority of patients are undiagnosed and diagnosis is often in specialist care at an advanced stage associated with significantly greater risk of liver-related mortality. Primary care support is ad hoc with an inappropriate reliance on liver function tests. We aimed to understand the current provision of UK NAFLD care pathways.
Method: Phase 1: rapid review and comparative analysis of national and international guidelines; database search of peer-reviewed UK publications and grey literature on NAFLD pathways. Phase 2: qualitative semi-structured interviews with key stakeholders identified using purposive and snowball sampling; framework analysis to identify key themes.

Figure 1: Map summarising pockets of good practice and key shareholders interviewed



Results: Phase 1: we found divergence across all three NAFLD guidelines (EASL 2016, NICE 2016 and AASLD 2018) throughout the recommendations for assessment, diagnosis and management. 27 UK publications on NAFLD pathways were identified. These identify pockets of good practice across the UK (fig 1): innovative, yet differing, pathways that transfer diagnosis from specialist to primary care and lead to earlier and increased diagnosis of patients. Phase 2: key themes identified from 25 interviews (fig 1) included: **1. Challenges:** (a) limited public and professional disease awareness; (b) conflicting guidelines; (c) paucity of evidence within primary care; (d) gaps in treatment pathway (eg licenced pharmacotherapy, lifestyle services); (e) inadequate integration with obesity/diabetes pathways; (f) limited workforce capacity and capability; (g) no sustainable funding for NAFLD pathways **2. Success factors:** (a) emerging evidence for using non-invasive stratification tools in primary care; (b) innovative IT solutions (eg patient assessment templates, automated pathology algorithms); (c) importance of local champions (GPs, hepatologists).
Conclusion: At present no single generalisable NAFLD pathway exists for national implementation. UK case studies show both effectiveness and cost-effectiveness of implementing local pathways. Wider roll-out of integrated NAFLD referral pathways will be crucial to maximise patient benefit once effective treatment options become available.

SAT308
The case for testing and treating all HBV patients

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Background and Aims: Every 30 seconds someone dies of complications associated with HBV, and, >95% of all HBV infections are in low and middle-income countries (LMIC) where access to diagnostics can be limited. In addition, with few exceptions, the patients are expected to pay for their own screening, lab tests and treatment in these countries. The current clinical guidelines use a combination of viral load, age, ALT, and HBeAg results to determine treatment eligibility. This study examined the impact of a test & treat strategy where all HBsAg+ individuals are treated.
Method: A literature search was conducted to find studies that report long-term HCC incidence in populations that follow the current guidelines and in HIV/HBV infected cohort where all HBV patients are put on treatment. A separate search was conducted for find studies that report the long-term adverse events of TDF and TAF in HIV patients. Finally, an economic model was used to estimate the cost of a test & treat strategy as compared to the current guidelines after taking into consideration loss to follow up.
Results: The limited available data suggest a lower incidence of HCC in the HIV/HBV cohorts, where all HBV patients are put on treatment, as compared to HBV mono-infected cohorts where the current guidelines are followed. The long-term adverse events of TDF were nominal with much fewer side-effects associated with TAF treatment. The economic impact analysis showed the loss to follow-up, and presentation with advance liver disease was much more expensive than test & treat-all approach.
Conclusion: A test & treat-all strategy may result in fewer HCC incidence and limited side-effects at a significantly lower overall cost. However, the risk of flare-up remains with intermittent treatment if patients discontinue and restart treatment. A test & treat strategy will require patient education programs to keep patients on chronic treatment.

SAT309
Opportunities to enhance linkage to hepatitis C care among people hospitalised for injection drug use-related complications: a population-based study

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Subgroup	ICD code	ICD-10 definition	long-stay/total hospitalisations, n	%
Recent drug dependence	F20.9	Schizophrenia, unspecified	1323/2454	54%
	F10.2	Dependence syndrome, alcohol	646/1753	37%
	F20.0	Paranoid schizophrenia	636/1035	61%
	F11.2	Dependence syndrome, opioid use disorder	570/1551	37%
	F25.9	Schizoaffective disorder, unspecified	570/944	60%
	F15.51	Psychotic disorder, stimulant psychosis	442/1578	28%
	F20.5	Residual schizophrenia	358/485	74%
	L03.13	Cellulitis of limb	230/669	34%
	F15.21	Withdrawal state, delirium	220/816	27%
	I33.0	Acute/subacute infective endocarditis	210/278	76%
Distant drug dependence	F20.9	Schizophrenia, unspecified	158/300	53%
	F10.2	Dependence syndrome, alcohol	134/496	27%
	F20.0	Paranoid schizophrenia	101/170	59%
	F25.9	Schizoaffective disorder, unspecified	86/167	51%
	F20.5	Residual schizophrenia	57/77	74%
	J44.0	Chronic obstructive pulmonary disease	51/256	20%
	C22.0	Hepatocellular carcinoma	40/199	20%
	J18.9	Pneumonia, unspecified	33/185	18%
	F25.0	Schizoaffective disorder, manic type	32/37	86%
	I50.0	Congestive heart failure	29/86	34%
No evidence of recent or distant drug dependence	C22.0	Hepatocellular carcinoma	109/706	15%
	F20.9	Schizophrenia, unspecified	77/115	67%
	F10.2	Dependence syndrome, alcohol	73/368	20%
	M17.1	Gonarthrosis (knee arthrosis)	73/639	11%
	J44.0	Chronic obstructive pulmonary disease	64/280	23%
	J18.9	Pneumonia, unspecified	51/256	20%
	F20.0	Paranoid schizophrenia	44/64	69%
	M16.1	Coxarthrosis (hip arthrosis)	41/329	12%
	I50.0	Congestive heart failure	40/108	37%
	F32.20	Severe depressive episode without psychotic symptoms	38/177	21%

Figure: (abstract: SAT309): Proportion of top ten ICD-10 primary diagnoses for long stay hospitalisations compared to total hospitalisations occurring 2015–2018 among people with HCV, by drug dependence.

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Background and Aims: To achieve HCV elimination by 2030, testing and treatment among high risk populations need to be enhanced. The primary aims were to: (1) characterise subpopulations of people with HCV based on indicators of recent and distant drug dependence during the direct-acting antiviral era (2015–2018) and (2) evaluate the potential for hospital admissions to improve linkage to HCV care among people with evidence of recent drug dependence.
Method: HCV notifications in New South Wales, Australia (1995–2017) were linked to opioid agonist therapy (OAT) (2001–2018) and hospital admissions (2001-June 2018) and deaths (1993–2018). Drug dependence was defined as injecting drug use-related hospitalisation (admissions occurring due to injectable drugs and/or injection-related infections) or receipt of OAT. Drug dependence occurring between 2015–2018 was considered as recent and 2001–2014 as distant. Primary diagnosis associated with each hospital episode was categorised using International Classification of Disease (ICD) version 10 major chapters, and re-categorised into cause-specific outcomes including mental health, drug, alcohol, and liver-related admissions occurring in 2015–2018.
Results: Among 90,590 people with HCV notification alive during 2015–2018, 20.4% (n = 19,376) had evidence of recent drug dependence, 22.4% (n = 20,280) had evidence of distant drug dependence, and 56.2% (50,934) had no evidence of drug dependence post-2001. Among those with recent drug dependence, 78.4% (n = 15,193) had been to hospital a total of 77,616 times (median 4 visits per hospitalised individual), compared to distant drug dependence, 36.9% (n = 7,485; 20,517 total visits, median 2 visits) and neither, 26.3% (n = 13,384; 33,668 total visits, median 2 visits) groups. Over the period 2015–2018, incidence of mental health (13.6 per 100PY), drug (19.04 per 100PY), alcohol (6.05 per 100 PY), and liver-related (4.20 per 100PY) hospitalisations were highest among those with recent drug dependence. 42.2% (n = 8,118) of those with recent drug dependence contributed to a total of 19,682 long-stay (≥7 days) hospital admissions, the majority due to mental and behavioural disorders, most commonly for schizophrenia (Figure).
Conclusion: Among people with HCV notification who have evidence of recent drug dependence, frequent hospitalisation – particularly mental health, drug, and alcohol admissions – presents an opportunity for engagement in HCV testing and linkage to care.

SAT310

Searching for patients lost in the system with chronic hepatitis C in a tertiary hospital: a problem still to be solved

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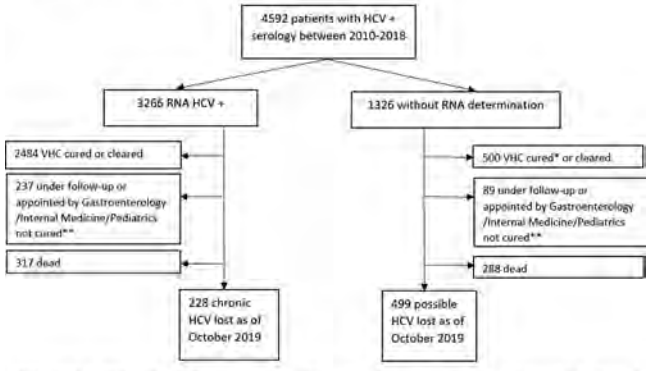
Background and Aims: Following the widespread use of direct-acting antivirals for the treatment of patients diagnosed with chronic hepatitis C, there is a growing interest in the elimination of this infection. Various strategies to detect undiagnosed patients have been recommended.

Method: Patients with positive HCV-antibody between 2010–2018 from our Microbiology laboratory (tertiary Hospital covering 660.000 healthcare population) were analyzed. Those with consecutive negative PCR-RNA HCV were excluded. The Hospital and Regional databases were reviewed and sorted as: 1) chronic HCV: last determination of HCV RNA available positive, 2) cured HCV: last determination of HCV RNA available negative after ≥12 weeks of end of treatment, 3) possible HCV: positive HCV serology without determination of HCV RNA available. Patients with chronic HCV or possible HCV without follow-up or scheduled with Gastroenterology/Internal Medicine were considered lost. A descriptive analysis of all variables was performed. The study was reviewed and approved by the center's Ethics Committee.

Results: 4592 patients with HCV positive serology were identified: 3266 with detectable RNA and 1326 without RNA determination. 677 patients (14.7%) lost in the system were detected: 61% male, 12% foreigner, 95% mono-infected (non-HIV), median age 54 years (45–69). The serological study of the lost patients was requested by Internal Medicine (11%), Gastroenterology (14%), Primary Care (33%) and other specialties (42%). Of the 677 lost patients, 288 had positive PCR-RNA HCV and 449 only positive serology. The classification of the remaining patients is shown in Figure 1.

Figure 1. Study patient flowchart



** Cured before 2010 or after 2018 in our center or in other centers/other Regional Healthcare Systems (data obtained through medical reports).*

*** Upcoming appointments, on-going treatment not currently finalized or decision of no treatment based in age, comorbidity, patient refusal, drug abuse, therapeutic poor compliance...*

Conclusion: Despite the widespread possibility of HCV treatment in Spain since 2015, there is a significant number of hepatitis C patients lost in the system. It is necessary to implement active detection strategies for these patients in order to achieve the goal of elimination.

SAT311

Economic evaluation of the hepatitis C virus screening and treatment program in Georgia

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Background and Aims: In spring 2015, the country of Georgia initiated an HCV elimination program with directly acting antivirals (DAA) donated by Gilead, alongside outstanding political commitment, and allocation of resources for a comprehensive program. We evaluated the cost-effectiveness of the screening and treatment undertaken in the HCV elimination program from 2015 to November 2017 compared to if no treatment had been done, from the perspective of the Ministry of Health (MoH) and patients.

Method: We adapted an HCV transmission and progression model calibrated to Georgian data on HCV prevalence and demographics of the general population and people who inject drugs (PWID) to project the impact of treatment of 41,483 patients during the study period. Quality adjusted life year (QALY) weights for liver disease stages including pre-cirrhosis, compensated and decompensated cirrhosis were estimated from EQ-5D-5L data collected from a subset of HCV-infected patients enrolled in the elimination program.

Unit costs were gathered from the financial module of the MoH on reimbursement schemes for healthcare providers. Cost of screening tests, diagnostics and monitoring during treatment, and the annual cost of care for patients with advanced liver disease, were then calculated per patient treated. Indirect costs of public awareness campaigns, infrastructure investment, administrative costs, and logistics were included as fixed costs. Case-finding costs were estimated based on the cascade of care. Estimated economic costs of DAA drugs (sofosbuvir and sofosbuvir/ledipasvir) were included in sensitivity analysis.

The incremental cost-effectiveness ratio (ICER) in terms of cost per QALY gained was calculated in 2015 US dollars accounting for all costs and outcomes from 2015–2030 with a discount rate of 3% for both costs and outcomes, and compared to a willingness-to-pay threshold of $3765 per QALY gained (1x GDP per capita in 2015).

Results: The total cost of screening and treatment per patient was $555. The average cost of liver disease care per patient was $416 with no treatment or $311 under the treatment scenario, with 0.78 QALYs gained per patient treated due to reduced disease progression. The intervention also prevented 2,673 HCV-related deaths and averted 16,225 new infections by 2030 compared to no treatment. The ICER of the intervention excluding DAA costs was $959/QALY, while including the cost of DAAs at a minimal generic cost of $143 per patient results in an ICER of $1,244.

Conclusion: The first phase of the HCV elimination program was highly cost-effective in Georgia. This provides valuable data on efficiency of national programmes for scaling up HCV treatment for achieving HCV elimination.

SAT312

Assessing the level of detection of hepatitis C virus RNA in individuals with detectable viremia following treatment with direct acting antivirals: and opportunity for new testing technologies

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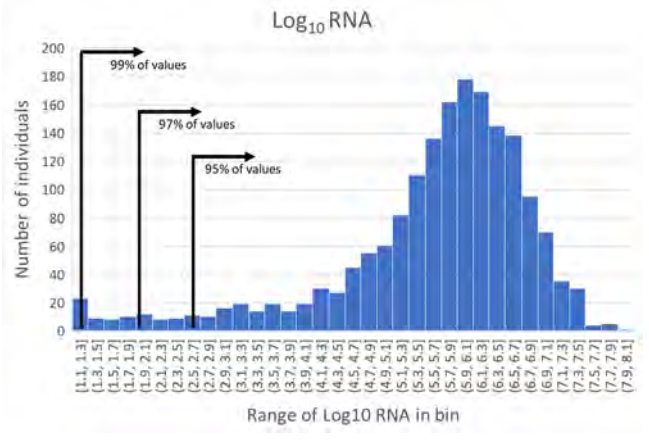
Background and Aims: Seventy five percent of the 130–150 million cases of chronic Hepatitis C Virus (HCV) infection in the world occur in low to middle income countries. The World Health Organization (WHO) has targeted HCV infection for elimination, but testing standards to confirm the success of treatment – sustained virologic response (SVR) – is a barrier to this goal. A low-cost, near-patient test is the highest priority target product profile in a global consensus process, and could streamline and potentially decentralize the testing process. To make a convincing argument to change the WHO pre-qualification level of detection (LOD) approval criteria requires characterizing the lowest reliable threshold to assess for SVR in those treated. Our aim is to better understand the level of HCV viremia after failing to achieve SVR and the characteristics of patients experiencing low-level detectable viremia after treatment with direct-acting antivirals (DAAs).
Method: We leveraged data from a large US cohort of veterans who underwent treatment to calculate the LOD for SVR. We used SVR testing data up to 24 weeks following the end of treatment to describe the range of HCV RNA levels found among patients with detectable viremia after DAA treatment completion. We characterized the HCV viral load distribution for individuals with detectable viremia and described the 95% 97%, and 99% percentiles of HCV RNA values – the level of HCV RNA below which treatment failure may be missed if a test could only detect that level of RNA. To better understand the types of patients who are at higher risk of being miscategorized as achieving SVR when they have low levels of detectable virus, we examined patients with the lowest 3% of the distribution of rebound HCV RNA. We conducted a logistic regression predicting low-level rebound viremia as a function of demographics including age, sex, race, and clinical characteristics of fibrosis stage, HIV co-infection, and HBV co-infection.
Results: Between January 2014 and March 2018 we identified 2,246 cases of detectable viremia following DAA treatment. Of those, 1,779 (79%) occurred within 24 weeks of the end of treatment. The 95th, 97th, and 99th percentiles of HCV RNA were 2.66, 1.97, and 1.25 $\log_{10}$ IU/mL, respectively with an associated distribution shown in the figure. In this sample, only age was significantly associated with experiencing low-level viremia on detection (OR = 0.96, 95% confidence interval 0.93–0.98).



Conclusion: While current HCV RNA testing can detect as little as 12 IU/mL of virus, our findings suggest that increasing the LOD to 100 IU/mL ($\log_{10}$ IU/mL = 2) or 450 IU/mL ($\log_{10}$ IU/mL = 2.7) would maintain good test accuracy, capturing 95% and 97% of detectable viremia cases following DAA treatment. These results should inform the development of more affordable portable tests for use in low- and middle-income countries.

SAT313

A population-based intervention to improve care cascade of patients with hepatitis C infection

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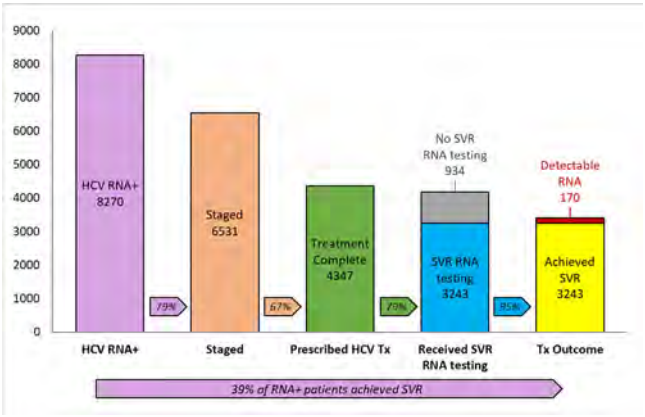
Background and Aims: Hepatitis C virus (HCV) infection is common in the general US population, leading to significant morbidity, mortality, and economic costs from chronic liver disease and hepatocellular cancer. New HCV infections increased nearly 300 percent from 2010 and 2015, and in 2012, HCV-related deaths surpassed deaths from all other reportable infectious diseases combined. However, simplified screening recommendations and highly effective direct acting antivirals for HCV present an opportunity to reverse this trend. We report the results of a community-based program to increase the testing, linkage to care, treatment and cure of persons with HCV infection.
Method: Public Health - Seattle & King County collaborated with three community health centers, three large multi-clinic health care systems (private, public and capitated), and an HCV patient education and advocacy group. Patients seen at least once at a partner clinical site were included. In order to increase screening of baby boomer patients (born during 1945–65), electronic health record (EHR) prompts and reports were created, as well as lower cost interventions such as birthday card reminders and posters. Case management linked patients to care. Primary care providers received education and training through class-room didactics, an online customized curriculum, specialty clinic shadowing and through a telemedicine program, Project ECHO. Data were extracted from partner EHRs to assess screening of baby boomer patients and monitor the progress of all diagnosed patients along the continuum of care during the project period (9/30/13–9/29/18).
Results: At baseline, 18% of baby boomer patients seen at partner primary care clinics had documentation of HCV testing; this proportion increased to 54% by the end of the project period. Of the 77577 baby boomer patients screened at 87 partner clinics, 2401 (3%) were newly HCV antibody positive. Among 8270 patients of any age with active HCV infection (RNA+), the majority were male (66%) and white (59%); 607 (7%) were HIV infected. The number of patients staged for treatment (either by genotype or a fibrosis test) increased by 391% during the project period and those treated increased by 1263%. Among the 79% of treated patients who were tested for sustained viral response (SVR), 95% achieved SVR.



Conclusion: A combination of EHR-based healthcare system interventions, active linkage-to-care, and educational and training strategies resulted in a tripling in the number of patients screened and more than tenfold increase of those treated. The interventions are scalable and foundational to the goal of HCV elimination.

SAT314

Do countries have the right policies to eliminate viral hepatitis B and C: a secondary analysis of the Lancet GastroHep viral hepatitis commission

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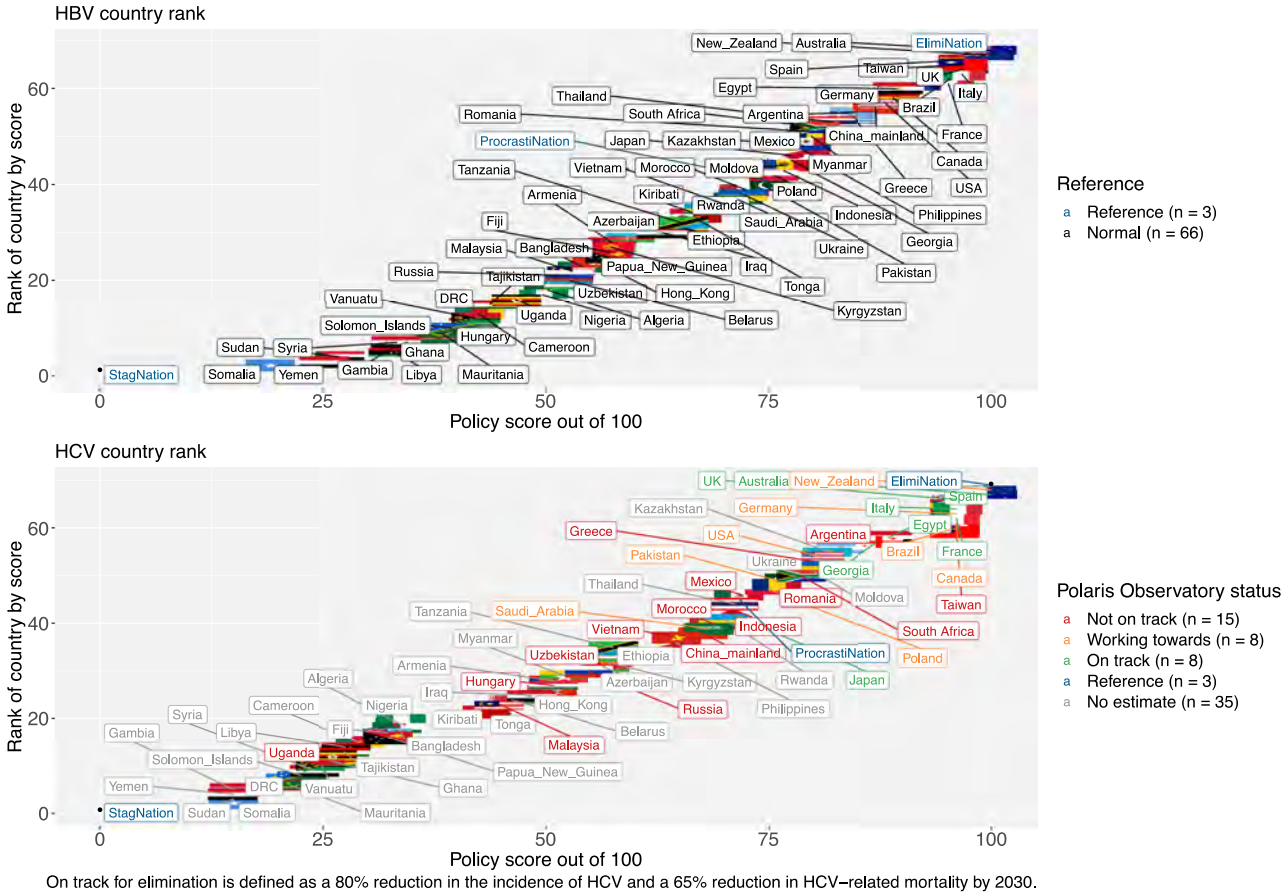
Background and Aims: In 2019, the Lancet Gastroenterology & Hepatology Commission reported on the status of 11 viral hepatitis policy indicators in 66 countries. Policies were reported as either being in place, in development, or not in place. Of the 11 viral hepatitis policies, 6 related to both hepatitis B virus (HBV) and hepatitis C virus (HCV), 3 policies applied only to HBV, and 2 policies were specific to HCV. This study used the commission findings to estimate country HBV and HCV policy scores and rankings.
Method: Two groups of variables were created: one for all policies relating to HBV and the other for all HCV related policies. We then applied a multiple correspondence analysis data reduction technique to each group of policies to reduce the policy indicators into a weighted summary of each possible different response to the policy indicators and generate scores for each country. Reference countries (StagNation, ProcrastiNation, and ElimiNation) were included in the analysis to help contextualize responses so that the minimum score was no policies and the maximum all policies. Values of the scores for countries were standardized to range from 0 to 100 (Best).
Results: The analysis estimated a summary factor that explained 58.1% of the variation for HBV and 70.3% for HCV. The highest scoring country for HBV was Australia while Somalia had the lowest score followed by Yemen and Sudan. For the HCV policy score, Australia and New Zealand had perfect scores while Somalia, Sudan, and Yemen had the lowest scores, all having only 1 indicator in place: mandatory screening of donated blood (Figure panel A). For HCV, countries were further analyzed by elimination status according to the Polaris Observatory (Figure panel B). Countries that were on track had a mean score of 91.4, countries that were working towards elimination had a mean score of 86.0, and countries that were not on track had a mean score of 66.1. Countries that did not have an estimate from Polaris had a mean score of 41.7 suggesting that a certain level of commitment is needed before a country receives a score.
Conclusion: In this study, we calculated HBV and HCV country policy scores for 66 countries. Countries that received higher scores had more policies in place than countries with lower scores. The index does not account for a country's disease burden and heavily burdened countries such as Nigeria, Russia, and Vietnam scored relatively poorly, despite having some policies in place.

Figure: Country (n = 66) HBV and HCV policy scores and rankings



On track for elimination is defined as a 80% reduction in the incidence of HCV and a 65% reduction in HCV–related mortality by 2030.

Figure: (abstract: SAT314)

SAT315

Validation of a novel rapid point-of-care ALT test in patients with viral hepatitis

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Background and Aims: Alanine aminotransferase (ALT) level is an important marker of liver inflammation. Limited access to laboratory resources makes ALT measurement challenging in low resource and remote regions. ALT1 protein antigen is cleared slowly from plasma than enzymatic ALT and is more stable at ambient temperature when stored for long periods outside cold chain. We validated a novel point-of-care (POC) ALT1 test in patients with viral hepatitis.

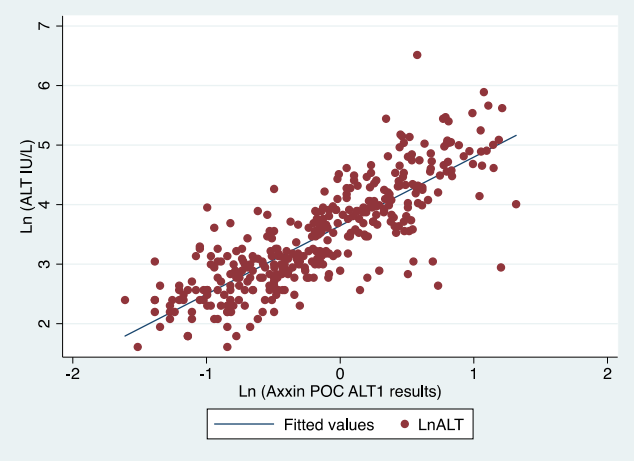

Figure: Linear regression plot of the association between ln (ALT) and ln (POC ALT1) values ($R^2 = 0.68$, $p < 0.0001$).

Method: The BioPoint® POC ALT1 test is an antigen immunoassay-based lateral flow test, which uses 40 μL whole blood or 15 μL plasma to provide ALT measurement two ways: 1. quantitative ALT result (Axxin handheld lateral flow reader) or 2. visual semi-quantitative result (cutoff 40 IU/mL), within 20 minutes. Quantitative POC ALT1 results were compared to standard laboratory assay ALT using Spearman correlation. A linear regression model was used to derive comparable values from POC ALT1 results (Axxin reader, arbitrary units) to standard ALT. Accuracy of POC ALT1 to detect ALT > upper limit of normal (ULN) was calculated by ROC analysis and agreement determined by Bland-Altman plot.

Results: 240 patients were included: 74 (31%) with hepatitis B and 166 (69%) with hepatitis C. 168 (70%) were male, mean age was 39 +/– 7.9 years and 18 (11.5%) had cirrhosis. Median ALT was 32 IU/mL (IQR 19–50).

Quantitative (Axxin Reader): There was moderate correlation between quantitative POC ALT1 results and ALT measured by laboratory assay ($R^2 = 0.68$; $p < 0.0001$). Derived POC ALT1 values had excellent accuracy for laboratory-based ALT > ULN in males and females. Bland-Altman plot showed a small mean difference 0.039 (95% CI –4.54–4.62) and significant variance difference (Pitman's test <0.0001).

Conclusion: The BioPoint® POC ALT1 test had good correlation with laboratory assay ALT and good accuracy for identifying hep B patients with ALT levels > ULN using AASLD and EASL criteria. Further validation of the POC ALT1 test in prospective clinical trials is needed.

SAT316

Cost-effectiveness of screening and treatment using direct-acting antivirals for chronic hepatitis C virus in low- and middle-income settings

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Background and Aims: Despite available direct acting antiviral (DAA) treatments for hepatitis C virus (HCV) infection, many people in lower- and middle-income countries (LMIC) remain undiagnosed and untreated. We assessed the cost-effectiveness of four HCV

Table: (abstract: SAT315)

Derived quantitative ALT results (Axxin reader)	AUC. (95% CI)	Sensitivity	Specificity	PPV	NPV
ALT > ULN*					
All	0.927 (95% CI 0.901–0.953)	92%	71%	80%	88%
Men	0.909 (95% CI 0.871–0.946)	92%	74%	80%	89%
Women	0.916 (95% CI 0.862–0.971)	93%	62%	79%	86%
ALT >2×ULN*	0.927 (95% CI 0.901–0.953)	87%	85%	69%	95%
All	0.923 (95% CI 0.895–0.959)				
Men	0.955 (95% CI 0.917–0.992)				
Women					
ALT >40 IU/mL**	0.929 (95% CI 0.901–0.956)	91%	84%	77%	93%

*ULN men 30 IU/mL, women 19 IU/mL; AASLD guidelines.
**ULN 40 IU/mL; EASL 2017 guidelines.
Semi-quantitative (visual read): Visual POC ALT1 results (cutoff 40IU/mL) had good accuracy for assay measured ALT > 40IU/mL (sensitivity 80%, specificity 82%, PPV 73%, NPV 87%).

Table: (abstract: SAT316)

Intervention	ICER	Threshold of 1x Gross Domestic Product per Capita	Cost-effective?	% Simulations Below Cost-Effectiveness Threshold
Cambodia: full model of care	$149/QALY	$1,270/QALY	Yes	100%
Cambodia: simple model of care	−$129/QALY	$1,270/QALY	Cost-saving	100%
Myanmar	$1,289/DALY	$1,299/DALY	Yes	51%
Pakistan	$488/DALY	$1,468/DALY	Yes	99%
Kenya	$805/DALY	$1,509/DALY	Yes	100%

screening and treatment programs implemented by Médecins Sans Frontières (MSF) in Pakistan, Myanmar, Cambodia and Kenya. The Myanmar intervention served HIV-HCV coinfected patients, Kenya served people who inject drugs (PWID), while Cambodia and Pakistan served the general population.

Method: The incremental cost-effectiveness ratio (ICER) was modelled as the cost (2018 US$) per disability-adjusted life year (DALY: Myanmar, Kenya, Pakistan) averted or quality adjusted life year (QALY: Cambodia) gained by HCV screening and treatment compared to no treatment from the provider's perspective over a life-time horizon. Cost and treatment outcome data were collected retrospectively from each program. Disease progression models were used for Myanmar, Cambodia and Pakistan, assuming low re-infection risk, while a dynamic HCV transmission model was used for Kenya because PWID have higher reinfection risk. The robustness of the projections were evaluated using deterministic and probabilistic sensitivity analyses.

Results: For current costs of DAA drugs in each setting ($120–524 per 12 week course of treatment), the ICER for each program varied from cost saving in Cambodia to $1,289/DALY averted in Myanmar, with mean ICERs all below country-specific thresholds for cost-effective interventions (Table). Higher laboratory and DAA costs in Myanmar increased the ICER compared to other settings. Kenya had high costs due to directly observed therapy but also had greatest impact due to the prevention benefit of treating PWID. Each country's ICER reduced most if the DAA costs were reduced or if the model of care was simplified with fewer visits and tests, and task shifting from doctors to nurses.

Conclusion: HCV screening and DAA treatment were shown to be cost-effective in four treatment programs in LMICs, supporting expanded access to HCV treatment in other LMICs.

SAT317

Cross-sectional associations between suspected non-alcoholic fatty liver disease, diabetes, and hypertension in hispanic adults living in the San Juan metropolitan area

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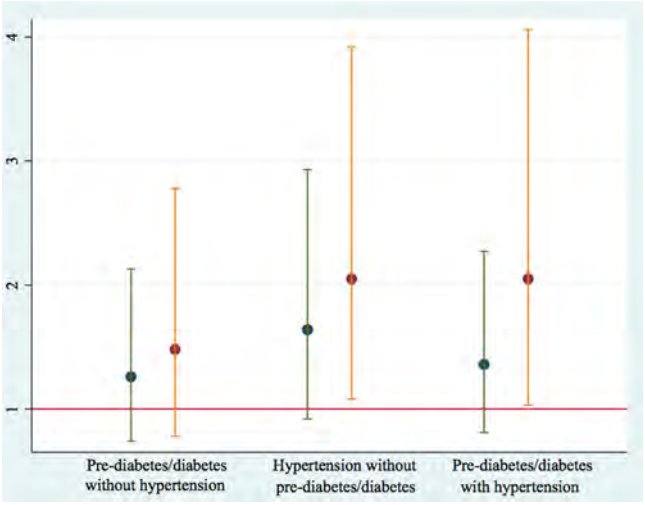
Background and Aims: Evidence suggests that there is a high prevalence of cardiometabolic diseases, such as diabetes and hypertension in Puerto Rico. These diseases have been directly linked to non-alcoholic fatty liver disease (NAFLD), yet there is no data available regarding the prevalence of suspected NAFLD among Puerto Ricans living in the archipelago. This study was undertaken to assess the prevalence of suspected NAFLD and its association with hypertension and pre-diabetes/diabetes among Puerto Rican adults living in the San Juan Metropolitan Area.

Method: A secondary data analysis of a household survey on diabetes and hypertension was performed. A total of 432 participants who had complete data on sociodemographic, behavioural, and cardiometabolic factors, including levels of aminotransferase, were included. Suspected NAFLD was defined on the basis of increased level of aminotransferase in the absence of excessive alcohol consumption. The estimated prevalence of suspected NAFLD was age-standardized using the 2010 USA population. In multivariate analyses, the associations between NAFLD and pre-diabetes/diabetes or hypertension status were adjusted for age, physical activity, waist circumference, triglycerides, high-sensitivity C-reactive protein, and alcohol consumption.

Results: The estimated age-standardized prevalence of NAFLD was 35.3% (95% CI: 28.2%, 43.6%) among women and 37.8% (95% CI: 29.0%, 48.5%) among men, with a statistically significant difference between groups ($p < 0.05$). In multivariate analysis, the estimated odds of having hypertension was 1.66 (95% CI: 1.05, 2.61) times greater for participants with suspected NAFLD relative to those without suspected NAFLD. Furthermore, in the multinomial logistic regression model, the estimated odds of having hypertension without pre-diabetes/diabetes among subjects with suspected NAFLD were 2.05 (95% CI: 1.08, 3.92) times the estimated odds among subjects without suspected NAFLD.



Conclusion: This study suggests that suspected NAFLD is highly prevalent among Puerto Rican adults living in the San Juan Metropolitan Area. Suspected NAFLD was positively associated with hypertension, but not with prediabetes/diabetes. Given the high prevalence of suspected NAFLD observed in this study, the replications of these findings could have substantial implications in the prevention of these chronic conditions.

SAT318

HCV care cascade of PWID enrolled in methadone substitution treatment program in Georgia - is this the first group of population in which hepatitis C will be eliminated in Georgia?

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Background and Aims: Since April 2015 Georgia has started hepatitis C elimination program with elimination goals by 2020. PWIDs enrolled in the Methadone Substation Treatment (MST) Program are also included in the large-scale screening program aimed to accelerate active HCV case detection. There are a total of 22 MST sites providing long term substation treatment to PWIDs in Georgia. HCV antibody screening is provided to patients at the enrollment in the MST program. The aim is to describe HCV care cascade among MST program beneficiaries.
Method: HCV care cascade was generated for the period of January, 2018 through October, 2019. The data linkage between MST database and national screening registry was done by matching national personal ID number. Cascade of care was generated using the matched data.
Results: Overall 9,552 PWIDs registered in MST database by November 1, 2019. A total of 8,265 (87%) MST patients had HCV screening of whom 7,041 (85%) tested positive and 5,998 (85%) were tested for viremia with the positivity rate of 85% (n = 5073). A total of 4,237 (83%) initiated treatment. By the date of the analysis 3,956 (93%) have already completed treatment of whom 3,808 (97%) were eligible for SVR. The cure rate among SVR tested was 96% (2,531/2,622).
Conclusion: The analysis of HCV care cascade for MST program beneficiaries shows high rates for screening and viremia testing uptake, treatment initiation and SVR rates. Meeting HCV elimination goals by 2020 is feasible however, requires more efforts.

SAT319

Screening and linkage to care of prisoners with HCV infection: the resist-HCV project

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Background and Aims: In prisons there is high prevalence of hepatitis C virus (HCV) infection, high rate of PWID and a substantial risk of HCV transmission. Epidemiological studies are needed to evaluate the rate of prisoners with chronic HCV hepatitis and to establish how many of them need Direct Acting Antiviral (DAA) therapy.
Methods: We conducted a cross-sectional study to explore the prevalence of HCV infection in all prisoners of Pagliarelli-Lorusso prison in Palermo (Sicily). At July 2019 prisoners received information on the virological test, the diagnosis of chronic hepatitis and the possibility of obtaining antiviral therapy inside the prison. Anti-HCV antibodies was detected by OraQuick HCV rapid oral test. Prisoners with positive screening performed serum HCV-RNA and viral genotype, evaluated liver disease stage by Fibroscan and received antiviral therapy. All prisoners signed an informed consent to use demographic, clinical and virological data. Chi-square test was used to analyze differences between groups.
Result: Among 1,147 prisoners (86.3% of entire population of the prison) who participated in the study, 1,139 (99.3%) accepted to perform oral test for HCV antibodies. Prisoners had a mean age of 42 ± 13 years without differences in 1,053 males (92.5%) and 86 females (7.5%). Overall, 55 prisoners (4.8%) resulted HCV antibody-positive: 46 out of 1,053 males (4.4%) and 9 out of 86 females (10.5%) ($p = 0.02$). Twenty-five out of 99 people (25%) who inject drug (PWID) and followed a program of opioid substitution therapy (OST) and 28 out of 1,040 no-PWID prisoners (2.9%) were anti-HCV positive ($p < 0.0001$). The prevalence of HCV antibodies was 22% (19/87) among males PWID and 50% (6/12) among females PWID ($p = 0.06$). Prisoners were more frequently infected with genotypes 1a (38.7%) or 3 (35.5%). Eleven out of 25 anti-HCV positive PWID (44%) and 16 out of 30 anti-HCV positive prisoners (53.3%) without history of drugs addict had a previous diagnosis of HCV infection ($p = 0.7$). Thirteen out of 27 prisoners (48.1%) with a previous diagnosis of HCV infection (6 of 25 PWID and 7 of 30 no-PWID) had already received a cycle of antiviral therapy.
Conclusions: Overall prevalence of HCV infection among prisoners is at least 4 times greater than in the general population and the main risk factor is a history of injecting drug use. About half of the prisoners with positive screening did not know their HCV infection. Only 36% of people with a known HCV infection had received antiviral therapy before arriving in prison. In prisons, it should be mandatory to program on-side screening for HCV infection and linkage to care patients with chronic liver disease.

SAT320

Frequency of prenatal hepatitis C screening and diagnosis in British Columbia, 2008–2018

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Background and Aims: Hepatitis C (HCV) is not part of routine prenatal screening in British Columbia (BC) Canada: pregnant people may be tested if they have risk factors or their prenatal care providers request HCV testing. We aimed to calculate frequency of prenatal HCV antibody testing and HCV diagnoses, as well as follow-up testing (RNA and/or genotype) among prenatally screened women in BC, from 2008–2018.
Method: We used BC Centre for Disease Control Public Health Laboratory (PHL) data linked with provincial surveillance data to estimate the number of women (female sex) aged 13–49 who received routine prenatal serological screening (HIV, hepatitis B, syphilis, and rubella) between 2008 and 2018. PHL performs >95% of all HCV screening tests in BC. HCV tests ordered on the same day as routine prenatal screens were considered prenatal HCV tests. Previously known HCV positive status was determined by HCV positive result prior to prenatal test. Seroconversion was a negative test at any time prior to a first positive test. Any follow-up RNA and/or genotype testing was assessed after prenatal anti-HCV screening.
Results: Prenatal HCV screening increased significantly from 2008 (Cochran-Armitage test for trend: $p < 0.001$), reaching nearly half of women receiving routine prenatal screening in 2018. Overall HCV prevalence among prenatally HCV screened women declined from 0.6% in 2008 to 0.36% in 2018. New HCV diagnoses due to prenatal HCV screening fluctuated over the ten year study period. Overall,

prenatal HCV screening identified 337 new HCV diagnoses, 24.3% were seroconversions and 75.7% were first time reactive results. In 2018, most women newly diagnosed with a prenatal HCV screen received follow-up RNA and/or genotype tests; 100% (9/9) of those who seroconverted and 90.1% (30/33) of those with first time reactive results; this compared to 82.5% (572/693) of all new HCV diagnoses among all women in BC the same year. Of 1,524 women who had previously tested HCV positive before receiving a prenatal HCV screen between 2008 and 2018, 97% had any RNA and/or genotype testing.

Figure: Proportion of all prenatal screens that included an anti-HCV test and number of women diagnosed anti-HCV positive as a result of a prenatal HCV screen, including new diagnoses (seroconversion or first time reactive) and previously known diagnoses (repeat testers) in BC, 2008–2018.

Conclusion: Risk-based prenatal HCV testing identifies undiagnosed HCV infections, and most women identified appear to be receiving appropriate follow-up testing. Further research is needed to understand differences in risk-based vs. routine prenatal HCV screening, as well as HCV vulnerability, infection, and care among pregnant women in BC.

SAT321

Re-capturing a lost population - the benefits of a nurse-delivered HCV community cirrhosis clinic

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Background and Aims: The current landscape of service provision for patients with liver disease does not match that of disease burden. A North London-based drug and alcohol dependency unit ('Better Lives') provides blood borne virus (BBV) screening and opioid substitution therapy (OST) as well as Hepatitis C Virus (HCV) treatment. These patients are often complex with marginalised social needs, have chaotic lifestyles and don't engage with conventional care models. We aimed to describe the demographics of a cohort of patients seen in a novel community outreach clinic (OC).
Method: Approximately 1000 patients per year receive OST from 'Better Lives' via a multidisciplinary clinic with doctors, nurses and recovery workers. 117 (11.7%) screened positive for chronic HCV. 22 (18.8% of chronic HCV patients, 2.2% of those receiving OST) with advanced liver fibrosis or cirrhosis (F3/F4) were referred to OC between November 2018 and September 2019. We used electronic hospital records to assess 'Did Not Attend' (DNA) rates to outpatient appointments (OPA) and emergency department (ED) attendances prior to review in OC and completion of key investigations afterward.
Results: 22 patients referred to OC in the study period (median age 52 (IQR 46.3–57), 81.8% male, 40.9% white). 14 patients (63.6%) attended. Chronic HCV primary aetiology in 12 (54.5%), 11 (50%) self-reported ongoing alcohol intake and 4 (18%) were people who inject drugs (PWID). Median liver stiffness 19kPa (IQR 12.95–36.1). 12 (54.5%) did not have registered GPs. 15 (68.2%) DNA hospital appointments prior to OC clinic.
Conclusion: This is the first UK-based nurse-delivered community liver cirrhosis outreach clinic aimed to improve treatment and supportive medical care and offer a link to hospital cirrhosis services. We re-engaged two-thirds of complex marginalised patients with advanced fibrosis via OC that would otherwise have been lost to follow up. Patients attending OC had an average of 2 prior DNA to hospital OPA and 6 ED attendances. 35% and almost 50% of patients had their surveillance US abdomen and gastroscopies, respectively, following attendance to OC compared with only 12% who did not attend. Further work to investigate if a community based liver outreach clinic can improve the trajectory of marginalised patients is required.

Table: (abstract: SAT321)

	All F3/F4 patients referred (n = 22)	Patients attending OC (n = 14)	Patients not attending OC (n = 8)
Age (median, IQR)	52 (46.3–57)	53.5 (45–57.75)	50.5 (28.5–53)
Gender (Male), n (%)	18 (81.8)	11 (78.6)	7 (87.5)
HCV Aetiology, n (%)	12 (54.5)	9 (64.2)	3 (37.5)
Ongoing alcohol intake, n (%)	11 (50)	11 (78.6)	0 (0)
Prior DNA OPAs, mean (SD)	2.14 (2.14)	2.07 (1.64)	2.25 (2.96)
Prior ED attendances, mean (SD)	5.05 (6.94)	6 (7.2)	3.38 (6.57)
US Abdomen after OC, n, (%)	7 (31.8)	6 (42.86)	1 (12.5)
Gastroscopy after OC, n (%)	6 (27.3)	5 (35.71)	1 (12.5)

SAT322

Strengthening HCV elimination policies through community-based research

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Background and Aims: Community-based approaches are known to be effective means of reaching marginalized populations that are not in contact with traditional health structures. Coalition PLUS–an international union of community-based NGOs involved in the fight against HIV and viral hepatitis–collaborated with partners in 5 low-middle income countries to carry out a study aimed at collecting data regarding HCV-related barriers encountered by communities in order to inform policies addressing HCV care and elimination in the targeted populations.

Method: Community-based research in an approach in which researchers and community actors collaborate at all stages of the research project: from identification of the research subject to dissemination of study results and advocacy. Community-based research applies rigorous methodologies to problems identified by and subsequent questions formulated through engagement with the communities affected by a given health issue.
Coalition PLUS applied these principles to the Mind the Gap (2018) study, a qualitative exploratory cross-sectional study in 5 countries included in the Unitaid-funded Coalition PLUS's HIV/HCV Drug Affordability project (India, Malaysia, Indonesia, Thailand, Morocco). Via surveys (240 focus group participants) and interviews (51 healthcare workers) with at-risk populations (people who inject drugs (PWID), former PWID, and people living with HIV) and healthcare workers, the study focused on gaps in the translation of HCV policies on paper into access to HCV services in practice.
Results: The study found insufficient HCV awareness among communities and insufficient HCV capacity in the health system. Participants described the HCV service pathway as too long, too complex, and too costly. For example, a majority of participants in several of the study countries highlighted the following as important service access barriers: travel distance, time off work, and costs. With these results, Coalition PLUS and partners approached the governments in the countries concerned and contributed to the following results:

12. Adoption of Standard Operational Practices for Hepatitis C by the MoH in Manipur stressing the importance of community care and of the specific needs of key populations;
13. Development of the discussion on simplification of diagnosis cascade in Morocco and India;
14. Development of a HCV service decentralisation pilot project in Malaysia.

Conclusion: The Mind the Gap study demonstrates how community-based research can serve as a key approach to evaluate problems, elaborate solutions, and advocate for evidence-based reforms. It is also a reminder of the importance of community engagement in the evaluation of policy impact and in the development of pertinent policies which meet the needs of those concerned. Building from this study, a second iteration of the Mind the Gap study will be launched in early 2020.

SAT323

Preliminary results of the prevalence of non-alcoholic fatty liver disease among the greater Toronto area population

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Background and Aims: The incidence and prevalence of NAFLD is on the rise. The natural history of this increasingly common condition is not well understood. Liver fibrosis is the most important predictor for morbidity and mortality among patients with NAFLD. This aim of this study was to undertake a retrospective analysis of the Fibroscan® results of a diverse patient population in the Greater Toronto Area (GTA) to understand the demographic composition of the population and the prevalence & severity of non-alcoholic fatty liver disease (NAFLD) within the GTA in Ontario, Canada, which is populated by individuals from different ethnic backgrounds.
Method: Retrospective review of 4486 charts was conducted in order to evaluate the status of fatty liver among a diverse patient population in the GTA. Patient geographical location, age, sex, fibrosis and steatosis scores were studied using descriptive statistics.
Results: Retrospective review of 4486 patient charts from the GTA revealed geographical distribution spanning 18 different cities/ regions in the GTA among 3147 patients. Of the study patients, 2344 male patients (52.3%) & 1860 female patients (41.5%) and in terms of age distribution: <30–1.9%, 30–39–7.3%, 40–49–16.9%, 50–59–28.3%, 60–69–26.4%, 70–79–15.1%, 80–89–3.2%, <90–0.2%. Fibroscan® results were registered in 3777 of the cases and the relative proportion of fibrosis staging was: F0–25.8%, F0 to F1–18.9%, F1–15.4%, F1 to F2–9.9%, F2–10.5%, F2-F3–4.6%, F3–4.1%, 3 to F4–2.7%, F4–8.2%. Steatosis results were available in 1759 of the 3777 available Fibroscan® results: S0–7.3%, S0-S1–3.0%, S1–14.1%, S1-S2–4.2%, S2–20.8%, S2-S3–13.8%, S3–36.8%.

Table 1: Patient Demographic Information

	Frequency	Percentage
Gender		
Female	1860	41.5
Male	2344	52.3
Age		
<30	85	1.9
30–39	326	7.3
40–49	759	16.9
50–59	1271	28.3
60–69	1185	26.4
70–79	678	15.1
80–89	145	3.2
>90	7	0.2
FibroScan® Results		
Fibrosis		
F0	973	25.8
F0-F1	712	18.9
F1	582	15.4
F1-F2	373	9.9
F2	398	10.5
F2-F3	173	4.6
F3	154	4.1
F3-F4	103	2.7
F4	309	8.2
Steatosis		
S0	129	7.3
S0-S1	53	3.0
S1	248	14.1
S1-S2	73	4.2
S2	366	20.8
S2-S3	243	13.8
S3	647	36.8

Conclusion: The majority of patients were between the ages of 50 and 69 and were male (52.3%). The Fibroscan® results range from no fibrosis to severe fibrosis/ cirrhosis. Moderate to severe fibrosis (F2-F4) was present in 30% of the patients, which cirrhosis (F4) was present in 8%. The majority of the charts where steatosis results were available reveal moderate to severe steatosis.

SAT324

Suboptimal linkage to care after identification of serum hepatitis B surface antigen-positive individuals in territory-wide screening: a need for educational and public health policies

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Background and Aims: Ensuring linkage to care is a key element to achieve the World Health Organization's goal of eliminating hepatitis B virus (HBV) as a public health threat by 2030. Data on linkage to care in chronic HBV patients under Asian health care systems remains lacking.
Method: Hepatitis B surface antigen (HBsAg)-positive individuals identified during a territory-wide hepatitis seroprevalence study in 2015–2016 in Hong Kong were referred to regional secondary care for further management. We assessed subsequent linkage to care using surveys conducted via telephone and text messaging. The first survey in 2018 focused on their follow-up status, reasons for refusing referral

among those without follow-up, and suggestions on improving linkage to care. The second survey in 2019 assessed their latest follow-up status, any active anti-HBV treatment and the presence of liver-related complications including cirrhosis and hepatocellular carcinoma (HCC).

Results: Among 10,256 Chinese participants from the initial seroprevalence study, we identified 803 HBsAg-positive individuals (7.8%), of which 382 (47.6%) had no prior knowledge of their HBV carrier status. 539 (67.1%) responded to the first survey, with 388 (72.0%) having active follow-up for their HBsAg-positive status. 279 (71.9%) were followed up at in the public sector, while 247 (63.4%) had received liver ultrasonography. Common reasons for patients refusing referral include: believing they were healthy and not requiring clinical care (38%), no available time (20.0%), lack of disease knowledge (12.6%) and long appointment waiting times (4.6%). Suggestions to improve linkage to care include text message reminders (43.0%), patient education programs (10.8%), availability of patient support groups (10.4%) and shortened appointment waiting times (1.7%). Among 402 individuals responding to our second survey, only 149 (37.1%) remained in active follow-up. 78 (19.4%) had commenced anti-HBV treatment, 10 (6.7%) had biochemical or radiological evidence of cirrhosis. Two patients had developed HCC, both detected during surveillance and were amenable to curative resection.

Conclusion: Post-screening linkage to care for chronic HBV patients remained suboptimal in Hong Kong, with low rates of engagement to clinical care and high rates of dropout. Considerable proportion of patients required treatment or developed complications. Systematic reminders and patient education coupled with timely referrals may facilitate linkage to care and prevent defaulting of follow-up.

SAT325

Changes in the hepatitis C cascade of care among individuals attending primary and community health services before and after the introduction of direct-acting antiviral treatment in Australia

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Background and Aims: Realisation of global hepatitis C elimination targets will require widespread access to treatment for people living with hepatitis C virus (HCV) as well increased testing among populations at risk of HCV infection, including people who inject drugs (PWID). We used sentinel surveillance data to explore HCV testing and changes in the hepatitis C cascade of care before and after universal access to direct-acting antiviral (DAA) treatment in Australia.

Method: De-identified clinical data were retrospectively extracted from eighteen primary care and community health clinics providing services targeted towards PWID and participating in the ACCESS surveillance project in the state of Victoria. Individuals were linked across clinics using a highly sensitive matching algorithm. We calculated the proportion of individuals attending a clinic who were tested for HCV antibodies and/or RNA, and the proportion of those tested with an RNA positive result, during the three-year periods immediately prior to (pre-DAA) and following (post-DAA) DAA introduction on 1st March 2016, as well as the total number of antibody tests in each period. Two cross sectional care cascades were then constructed to classify all individuals ever diagnosed RNA-positive as having reached one of four cascade stages by 28th February 2016 and 28th February 2019, respectively; (1) diagnosed RNA-positive; (2) HCV genotype/viral load tested; (3) treated within the clinic network; and (4) evidence of cure (RNA negative ≥48 weeks [interferon treatment] or ≥8 weeks [DAA treatment] post treatment initiation).

Results: Of the 113,248 individuals visiting a clinic in the pre-DAA period, 13,784 (12.2%) had an HCV test, of whom 1,918 (13.9%) had a positive RNA result, within the period. Of the 139,082 individuals visiting a clinic in the post-DAA period, 14,507 (10.4%) had an HCV test, of whom 2,070 (14.3%) had a positive RNA result, within the period. The total number of antibody tests conducted was 14,267 and 14,236 in the pre- and post-DAA periods, respectively. The February 2016 care cascade included 2,515 individuals ever RNA-positive of which; 1,977 (78.6%) were viral load/genotype tested; 19 (0.8%) initiated treatment; and 12 (0.5%) had evidence of cure. The February 2019 care cascade included 3,713 individuals ever RNA-positive of which; 3,276 (88.2%) were viral load/genotype tested; 1,674 (45.1%) initiated treatment; and 863 (23.2%) had evidence of cure.

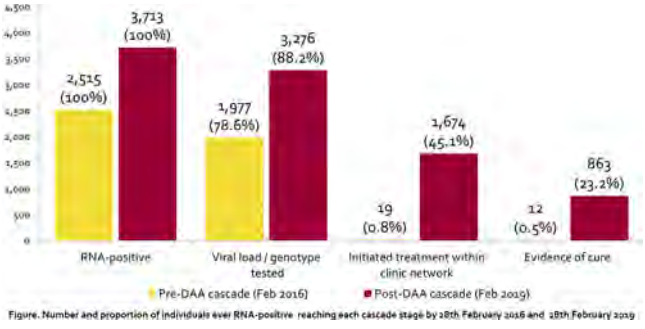

Figure. Number and proportion of individuals ever RNA-positive reaching each cascade stage by 28th February 2016 and 28th February 2019

Conclusion: Marked improvements in the cascade of hepatitis C care among patients attending this network of primary care clinics were observed following the universal access of DAA treatments in Australia, although antibody testing remained stable across periods. Increased diagnostic testing will be necessary to identify individuals chronically infected with hepatitis C to maintain adequate levels of treatment uptake and achieve elimination.

SAT326

Microelimination of chronic hepatitis C in Romania - another pathway to achieve national elimination goals by HepC ALERT project

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Background and Aims: There is consensus in the application of micro-elimination for achieving HCV eradication worldwide that is why we adopted it in Romania, a country with a previously known high prevalence. The aim of our study was to perform screening of

HCV in specific populations in certain sub-regions of Romania and link them to treatment right away after diagnosis.
Method: We conducted a screening program by Gastroenterology specialists from 4 different Regions of Romania. Screening was offered to all patients admitted into the hospital Departments. We used rapid diagnostic tests, the positive HCV Ab subjects were further evaluated for viral load and fibrosis and antiviral treatment was started immediately. A questionnaire with 17 questions was given at the time of testing in order to identify risk factors for HCV infection.
Results: Between March and November 2019, 17497 persons were screened. Overall 1.45% had a positive HCV test, with the highest prevalence in Cluj (1.84%) and the lowest in Bucharest (1.26%). Patients found positive were older (64.9 ± 12.8 vs 52.2 ± 16.8years, $p < 0.0001$), from rural areas (2.36% rural vs 1.17% urban, $p < 0.0001$), with a higher prevalence in the Gypsy population (3.67% Gypsy vs 1.46% Romanians and 0.76% Hungarians, $p = 0.16$). In patients with positive HCV the following risk factors were identified in a significantly higher proportion: previously known infection with HBV/HDV, blood transfusions and unsafe abortions before 1990, multiple surgical interventions and multiple hospitalizations during lifetime, multiple stomatology interventions and IV drug users.
Conclusion: During the HEPC A.L.E.R.T. micro-elimination program in Romania, a viremic prevalence of 1.45% was detected, significantly lower compared to the previous reported data. Testing all out- and in-patients attending different departments of regional hospitals might be an efficient approach of screening and link to care cascade of hepatitis C management.

SAT327

What is required for achieving HCV elimination in Singapore? A modeling study

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Background and Aims: Singapore is a country with a low general population HCV seroprevalence (0.37–0.54%). The vast majority of hepatitis C virus (HCV) infection in Singapore is among those with a history of injecting drug use (IDU, 45% of whom having history of current or past HCV infection), yet what is required to achieve the World Health Organization (WHO) HCV elimination targets (80% incidence reduction, 65% mortality reduction by 2030) is unknown. We model the intervention scale-up and targeting required to achieve WHO targets in Singapore.
Method: A dynamic model of HCV transmission and progression among those with a history of IDU was calibrated to Singapore, a setting with approximately 11,000 people with a history of IDU in 2017 and recent declines in IDU (based on a decline in arrests of new heroin users by ~30%/year from 2012–2018), among whom 45% are seropositive for HCV. We projected HCV treatment scale-up from 2019 required to achieve the WHO targets with varying treatment targeting scenarios (no prioritization, prioritize PWID, prioritize cirrhotics, prioritize PWID and cirrhotics). We explored the impact of opiate substitution therapy (OST) implementation (to 40% among PWID) on treatments required.
Results: In 2019 in Singapore, there were an estimated 3855 (95% CI:2635–5446) chronically HCV infected individuals with a history of IDU and 148 (95%CI: 87–284) incident HCV cases. To reach the HCV incidence target in Singapore, 272 (95%CI 187–384) treatments are required in 2019, totaling 2444 [95%CI 1683–3452] across 2019–2030. By prioritizing PWID or PWID and cirrhotics, 60% or 30% fewer treatments are required, respectively, whereas the target cannot be achieved with cirrhosis prioritization. OST scale-up could reduce treatments required by 21–24% depending on treatment targeting. Achieving both WHO targets requires treating 631 (95%CI: 359–1047) in 2019, totaling 3816 (95%CI: 2664–5423) across 2019–2030. Similar 2019 treatments but fewer cumulative treatments are needed if prioritized to PWID and cirrhotics.
Conclusion: HCV elimination is achievable in Singapore, but even in a setting of declining IDU requires immediate treatment scale-up among PWID. Combination harm reduction and treatment could reduce treatments required and provide additional benefits.

SAT328

Hepatitis C virus screening of people with severe mental illness: a cost-effectiveness analysis

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Background and Aims: Hepatitis C virus (HCV) has been shown to be more common among people with severe mental illness (PSMI) than in the general population, with a prevalence ranging between 4.6–17.4%, compared to 0.5–2.3% in the general population worldwide. Moreover, HCV prevalence in the PSMI population with a history of drug abuse screened at the Psychiatry department at the Geneva University Hospitals (Psy-HUG) was estimated to be 25.7%. We aim to assess a generalized screening approach of all PSMI, including those without a history of drug abuse with a prevalence of 3.49%.
Method: Prevalences were estimated from unpublished anonymous data obtained from the HUG electronic patient record. The inclusion criteria were all patients hospitalized at Psy-HUG from January 2016 until July 2019 who were screened either for antibodies to HCV, or HCV RNA from 1990 onwards. To identify PSMI with a history of substance abuse, text data mining techniques employing natural language processing were used to search for terms such as 'heroin', 'methadone' or 'cocaine' in the patient electronic records. This study adapted a previously published cohort decision tree screening model to estimate the cost-effectiveness of routine PSMI HCV screening compared to the current risk-based screening approach (i.e. only PSMI with a history of drug abuse).

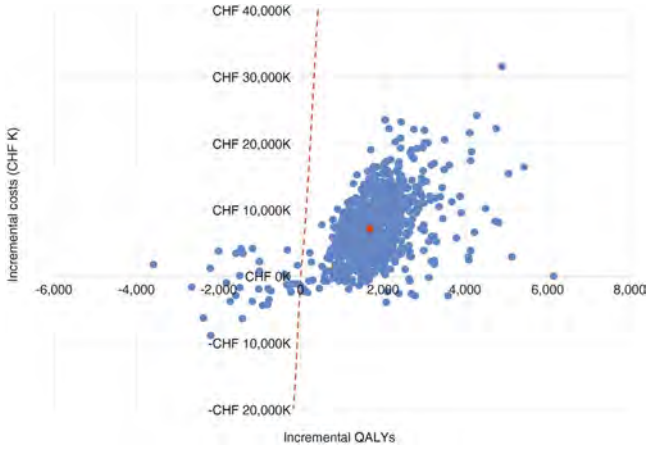

Figure: Scatter plot of the probabilistic sensitivity analysis on the cost-effectiveness plan.

Results: The total population size was 4,548. Generalized PSMI screening was found to be cost-effective compared to current risk-based screening, with a base-case incremental cost-effectiveness ratio of CHF 4,217 per quality-adjusted life year (QALY). The total incremental cost of the generalized screening programme at the

population level was CHF 7,360,028. The results of a probabilistic sensitivity analysis of 1,000 model simulations showed that 96.4% of simulations predicted generalized screening of PSMI to be cost-effective at the willingness-to-pay threshold of CHF 100,000 per QALY (Figure).

Conclusion: Accrued screening and treatment of HCV-infected individuals, particularly in higher prevalence population subgroups, is necessary to reduce the global burden of HCV and move towards the World Health Organization's goal of viral hepatitis elimination by 2030. Model results show that generalized screening of PSMI is cost-effective compared to current risk-based screening at a range of WTP thresholds, demonstrating that screening for HCV of all PSMI should be considered by Swiss policy-makers.

SAT329

Incidence of HCV infection among gbMSM in British Columbia, Canada: a population-based cohort study

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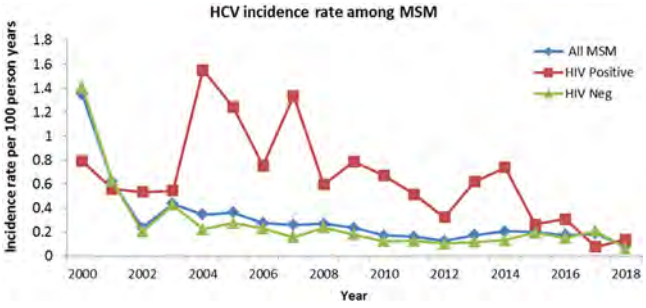
Background and Aims: Gay, bisexual, and other men who have sex with men (gbMSM) are at high risk of HCV infection. Monitoring incidence of HCV among gbMSM is critical to achieve hepatitis elimination goals. However, there is lack of data from the population-based systems to monitor incidence of HCV among gbMSM. In this study, we estimated the incidence of HCV infection among gbMSM in a large population-based cohort in Canada.

Method: This analysis included all gbMSM in the BC Hepatitis Testers Cohort (BC-HTC) who have been tested for HCV at least twice between Jan 1, 2000 and Dec 31, 2018, with a first test being negative. Incident HCV infection was defined as a positive anti-HCV, RNA, or genotype test following a negative anti-HCV test among gbMSM. gbMSM were identified based on self-report. Status for those with missing information was imputed based on a validated algorithm with 95% specificity. Annual incidence rates for HCV infection from 2000 to 2018 were estimated and Cox proportional hazards models were constructed to identify risk factors associated with HCV infection among gbMSM.

Results: Among 44,172 eligible gbMSM, 641 HCV seroconversions occurred over 286,253 person-years (PY) of follow-up with an overall incidence rate of 0.22/100PY (95%CI: 0.21–0.24). The incidence rate was highest among gbMSM with drug dependence (1.44, 95%CI: 1.28–1.61), especially those with history of opioid misuse (2.45, 95% CI: 2.07–2.9) and stimulant misuse (1.79, 95%CI: 1.53–2.1). Incidence declined from 1.3/100PY in 2000 to 0.078/100PY in 2018. In the multivariable model, younger birth cohorts (1965–1974: adjusted hazard ratio (HR) 7.54, 95%CI: 3.1–18.37; ≥1975: HR 13.7, 95%CI: 5.64–33.23 compared to <1945), history of drug dependence (HR: 5.56, 95%CI: 4.44–6.98), opioid misuse (HR: 2.08, 95%CI: 1.61–2.68), HIV coinfection (HR: 4.38, 95%CI: 3.61–5.31), and material deprivation (most privileged vs most deprived: HR: 0.55, 95%CI:0.45–0.68) were associated with HCV seroconversion. In models stratified by HIV status, drug dependence and opioid misuse were not significantly associated with HCV seroconversion risk in people with HIV infection.

Conclusion: Overall incidence rate among gbMSM is low, consistent with previous data, with high incidence among those with drug use. gbMSM with HIV infection, drug dependence, opioid misuse, and material deprivation are at higher risk of HCV infection, requiring multi-faceted approaches to reduce the risk of HCV infection among gbMSM subgroups.



SAT330

An OST (opiate substitution therapy)-based hepatology service facility (OHSF) with access to chronic hepatitis C treatment: the example of an one stop shop as a practical step towards HCV elimination in patients who use drugs (PWUD)

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Background and Aims: Direct Acting Antivirals (DAAs) have improved efficacy and tolerability in the treatment of chronic hepatitis C virus (HCV) infection. However, access is often limited in PWUD patients receiving OST, who may be underserved for health care and face social inequity. We determined the effectiveness of an OST-based hepatology service facility (OHSF) with access to HCV evaluation and treatment.

Method: We prospectively enrolled 265 anti-HCV patients (M/F: 216/49, mean age: 43.2 ± 9.2 years) who have been referred by other OST programs between September 2018 and September 2019. The services provided by the OHSF include complete biochemical evaluation, HCV, HBV and HIV virology screening, access to HCV RNA/Genotype evaluation and liver stiffness measurement (LSM).

Results: 258/265 (97.5%) were Greeks, 36/265 (13.5%) cirrhotics, 35/265 (13%) treatment experienced, 8/265 (3%) HIV positive and 6/265 (2.5%) were HBsAg positive. In total, 217/265 (82%) of the patients underwent HCV RNA/Genotype evaluation and 185/217 (70%) were viraemic with the following genotype distribution: G1a: 23%, G1b: 3%, G2: 2%, G3a: 58.5% and G4: 13.5%. HCV RNA/Genotype evaluation was not initiated more frequently in HIV-positive than in HIV-negative patients [5/42 (12%) vs 3/198 (1.5%), p = 0.005]. Finally, 183/185 (99%) of the viraemic patients have been scheduled for HCV treatment. Treatment initiation was recorded in 144/183 (79%) patients. None of them has been lost in follow-up: 127/144 (88%) have completed the treatment while 17/144 (12%) are still under treatment.

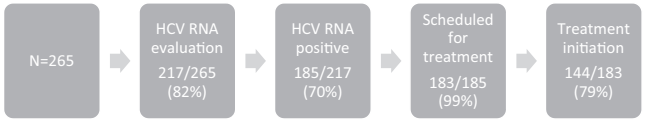

Figure: Treatment scale initiation among OST patients referred at OHSF.

Conclusion: A significant proportion (>75%) of anti-HCV positive patients referred at OHSF with access to chronic hepatitis C treatment receive antiviral treatment. HCV RNA/Genotype evaluation starts significantly less frequently in HIV-positive patients. The vast majority of OST patients referred at OHSF (>80%) will complete treatment.

SAT331

Recent decline in hepatocellular carcinoma rates in the United States

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Background and Aims: In the United States, rates of hepatocellular carcinoma (HCC) increased over several decades and were projected to increase ~3%/year through 2030. Here, we provide HCC rates through 2016.

Method: HCC incidence data were obtained from SEER-21, a group of population-based cancer registries covering 37% of the U.S. population. Cases were identified using International Classification of Diseases for Oncology, 3rd edition codes (site: C22.0; histology: 8170–8175).

Incidence rates were age-standardized to the 2000 US population, and estimated overall and by sex, age group and race/ethnicity. Annual percent changes (APCs) were estimated using joinpoint regression, which identifies statistically significant inflection points in rate trajectories. Rate ratios (RRs) comparing 2016 to 2015 were estimated.

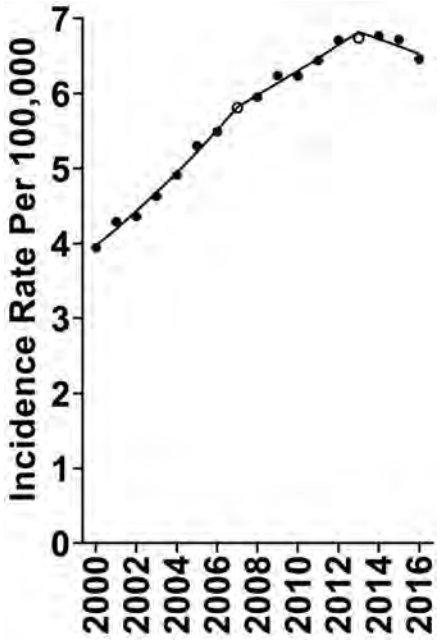

Figure 1: Hepatocellular carcinoma incidence rates in 21 US cancer registries, by year – 2000 to 2016. Open circles indicate joinpoints where the annual percent change differs significantly from zero at the alpha = 0.05 level.

Results: Figure 1 shows that overall HCC rates increased 5.64%/year during 2000–2007 ($p < 0.001$), 2.68%/year during 2007–2013 ($p < 0.001$) and then plateaued starting in 2013 (APC = -1.44%/year; $p = 0.12$). HCC incidence was significantly lower in 2016 compared to 2015 (RR = 0.96; $p = 0.007$).

HCC trends differed by age. Inflections and significant decreases occurred among 35–49-year-olds starting in 2006 (APC = –4.93%/year; $p < 0.001$) and among 50–64-year-olds starting in 2014 (APC = –6.64%/year; $p = 0.04$). For ≥65-year-olds, rates increased during the entire time period (APC = 2.69%/year; $p < 0.001$).

By race, HCC rates plateaued among Whites beginning in 2013 (APC = –0.91%/year; $p = 0.45$) and among Blacks in 2009 (APC = 0.27%/year; $p = 0.65$). Among Hispanics, HCC incidence decreased beginning in 2014 (–6.55%/year; $p = 0.08$) and was significantly lower in 2016 than 2015. Among Asians, starting in 2007, HCC rates decreased –2.72%/year ($p < 0.001$). In contrast, for American Indian/Alaska Natives, HCC rates increased 4.60%/year ($p < 0.001$) across the entire time period.

Conclusion: U.S. HCC incidence increased for decades and was projected to continue rising through 2030, however, recent data indicate HCC rates flattened in 2013 and then declined in 2016. Our analysis suggests the tide has begun to turn for HCC incidence in the United States.

SAT332

HCV screening and linkage to care of homeless people in a major European city. Data from a mobile screening unit (MSU)

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Background and Aims: Homeless people have a higher prevalence of HCV than general population. Due to their life-style, homeless people are in an unfavorable situation to access screening, diagnosis and treatment of any infectious diseases. The aims of this study were to calculate the prevalence of HCV active infection in homeless people in a mayor European city and to evaluate the impact of using a mobile screening unit (MSU) and navigators on the linkage to HCV care in this population.

Method: By means of an MSU and an interdisciplinary health team, those places in Madrid where vulnerable populations gather were detected. From 2/2019–11/2019, HIV, HCV and HBV rapid tests were conducted in these locations. Participants who tested positive, were tested for RNA-HVC using Xpert at the MSU. Those with an active infection were offered referral and accompaniment to their hospital. Descriptive, bivariate and multivariate analysis was used to compare homeless and no homeless people.

Results: During the period of study, the MSU screened 1577 subjects and 1028 (65%) of them were homeless. Of the total number of homeless people, 712 (69%) were male, median age was 43 years, 587 (57%) were from abroad, 256 (67%) had consumed drugs (heroin or cocaine) in the last year, 177 (46%) were in opiate substitute treatment, 275 (27%) consumed alcohol (>50 g/day) and 191 (19%) used benzodiazepines. Of the total homeless people screened, 197 (19%) had a positive HCV rapid test and, 71 (39%) of them had active HCV infection, 59 (6%) had HIV infection (5% new diagnosis). Globally, 59 (85%) patients were referred to a hospital and 44 (62%) initiated HCV treatment.

Homeless people were more frequently born outside Spain (57% vs. 25%, $P < 0.001$) than those who were not homeless. Homeless people were also more frequently evaluated by a hepatologist than those who were not homeless (85% vs. 24%, $P = 0.042$). There were no statistically significant differences in those who initiated HCV therapy (>80% of treatment initiations). Median time to treatment initiation was 38 days.

Conclusion: Active hepatitis C infection remains prevalent in vulnerable populations, particularly in the homeless population. A strategy that uses a mobile unit, improves access to HCV care even in difficult-to-reach populations.

SAT333

Development of a supportive needs assessment tool for cirrhosis (SNAC)

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Background and Aims: Accurate assessment of the supportive needs of individuals with cirrhosis is important to improve patient care. To address the lack of a specific health needs assessment instrument for this patient group, we developed what is, to the best of our knowledge, the first supportive needs assessment tool for cirrhosis. We report the development and psychometric testing of a Supportive Needs Assessment tool for Cirrhosis (SNAC).

Method: The SNAC was developed in three stages, namely: (i) item generation; (ii) pre-testing of the first draft of the SNAC (face and content validity, review, and field-testing of the instrument); and (iii) psychometric evaluation of the newly developed SNAC (Fig). The 50-item SNAC was administered to patients (n = 465) diagnosed with cirrhosis recruited from five metropolitan hospitals in Queensland, Australia. Items were assessed for ceiling and floor effects, and exploratory factor analysis was used to assess the factor structure. Identified factors were assessed for internal consistency and convergent validity to validated psychosocial tools.

Results: Exploratory factor analysis identified 4 factors (39 items), which together accounted for 49.2% of the total variance. The 39-item SNAC met the requirements of a needs assessment tool and identified a range of needs important to patients with cirrhosis that were grouped in four subscales: 'Psychosocial issues', 'Practical and physical needs', 'Information needs', and 'Lifestyle changes'. Cronbach alpha for the total scale was 0.94; values ranged from 0.64 to 0.92 in all subscales. Convergent validity was supported by a strong correlation between the total SNAC score and that of the Chronic Liver Disease Questionnaire (CLDQ; Spearman rho –0.68; $p < 0.001$), and moderate correlations with the Distress Thermometer (Spearman rho 0.53; $p < 0.001$) and seven subscales of a generic health-related quality of life instrument (Short Form 36; Spearman rho ranged from –0.48 to –0.57; $p < 0.001$). The SNAC discriminated patient groups with respect to gender ($p = 0.013$), age group ($p < 0.001$), and hospital admission status (admitted vs. not; $p < 0.001$).

Conclusion: These data provide initial evidence for the validity and reliability of the SNAC, an instrument designed to measure the form and amount of perceived unmet practical and psychological needs of patients with cirrhosis.

SAT334

Inequities in presentation and outcomes for indigenous Australians hospitalised for cirrhosis

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Background and Aims: Indigenous Australians experience greater health disadvantage and have a higher prevalence of many chronic health conditions compared to other Australian adults. Liver diseases are among the most common contributors to the mortality gap between Indigenous and other Australian adults. However, differences in presentation and patient outcomes between Indigenous and non-Indigenous Australians hospitalised with cirrhosis have not been investigated.

Method: Using data from the Hospital Admitted Patient Data Collection and the Death Registry, this retrospective, population-based, cohort study including all people hospitalised for cirrhosis in the state of Queensland during 2008–2017 (779 Indigenous and 10,642 non-Indigenous) examined rate of readmission (Poisson regression), cumulative survival (Kaplan–Meier), and assessed the adjusted differences in survival (Multivariable Cox regression) by Indigenous status.

Results: A higher proportion of Indigenous patients were younger than 50 years (346 [44%] vs. 2,063 [19%] non-Indigenous patients), lived in most disadvantaged areas (395 [51%] vs. 2,728 [26%]), had alcohol-related cirrhosis (547 [70%] vs. 5,041 [47%]), had ascites (314 [40%] vs. 3,555 [33%], and presented to hospital via the Emergency Department (510 [68%] vs. 4,790 [47%]). Compared to non-Indigenous patients, Indigenous patients had 3.04 times the rate of non-cirrhosis readmissions (95%CI 2.98–3.10) and 1.35 times that of cirrhosis-related readmissions (95%CI 1.29–1.41), and lower overall survival (17% vs. 27%; unadjusted hazard ratio (HR) = 1.16 95%CI 1.06–1.27). In multivariable analysis, adjusting for age group increased the HR to 1.30 (95%CI 1.18–1.42). Most of the survival deficit was explained by Emergency Department presentation (adj-HR = 1.03 95%CI 0.93–1.13), and alcohol-related aetiology (adj-HR = 1.08 95%CI 0.99–1.19). The remaining survival deficit was influenced by the other

Figure: (abstract: SAT333): Overview of the stages of development of the Supportive Needs Assessment tool for Cirrhosis (SNAC).

clinico-demographic factors and health service use (final adj-HR = 1.08 95%CI 0.96–1.20).
Conclusion: There was evidence of differential presentation, higher rates of readmissions, and poorer survival for Indigenous Australians with cirrhosis, compared to other Australians. The increased prevalence of Emergency Department presentation among Indigenous patients suggests missed opportunities for early intervention to prevent progressive cirrhosis complications and hospital readmissions.

SAT335
Leveraging direct-to-patient messaging: electronic record assimilation and subsequent eradication of hepatitis C (Erase-C)
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Background and Aims: Hepatitis C virus (HCV) screening is a crucial step in HCV elimination. Currently, the United States Preventive Services Task Force recommends a one-time HCV screen in individuals born between 1945 and 1965 (henceforth baby boomer birth cohort, BBBC). Adherence to this guideline in the US population is 14% and within the Stanford primary care clinic, 18%. Direct-to-patient messages via electronic medical record (EMR) improves adherence to other healthcare maintenance recommendations, but has not been studied for HCV screening. We aim to study the efficacy of a direct patient message via EMR in improving HCV screening rates within a large US healthcare system.
Method: Randomized study comparing the effectiveness of a direct-to-patient electronic health message on HCV screening coupled with a lab requisition, versus HCV screening initiated by primary care (PC) clinicians in an unscreened BBCC. Patients were stratified into two strata based on whether they had a PC appointment in the upcoming 6 months. Within each stratum, 400 patients were randomized to receive a one-time EMR message on HCV screening, coupled with a lab requisition for HCV antibody and 400 patients did not receive a message. Patients were followed for six months and rates of HCV screening compared between groups.

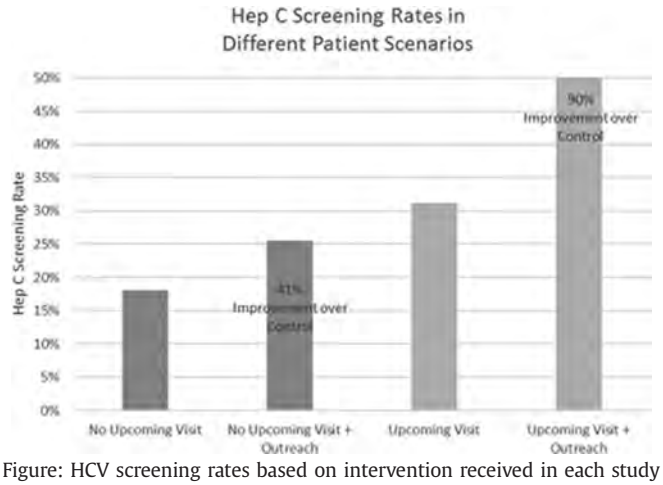

Figure: HCV screening rates based on intervention received in each study cohort.

Results: During the six months intervention period, 598 of 1600 (37.4%) baby boomers in the study cohort had HCV screening test performed. Screening rates were highest at 60.6% among those that received a message *and* had an upcoming PC appointment compared to 34.8% in those that did not receive a message ($p < 0.01$). Similarly, in the stratum without an upcoming PC appointment, HCV screening rate among those that received a message was 30.8% compared to 20.3% in those that did not receive a message ($p < 0.01$; Figure 1). The greatest impact in the cohort with an upcoming PC appointment was seen in patients that had an appointment within three weeks of message being sent. Among 598 screened patients, there were no positive HCV antibody results.
Conclusion: Direct-to-patient messaging via EMR is an effective way of improving HCV screening uptake in unscreened BBCC that is established within a healthcare system. Messaging should ideally occur within three weeks of a patient's upcoming clinic appointment.

SAT336
Catalytic funding of viral hepatitis elimination program in Uzbekistan
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Email: rdunn@cdafound.org.

Background and Aims: Globally, >95% of all HBV infections and >80% of all HCV infections are in low and middle-income countries (LMIC). Except for a handful of countries, most cannot afford to pay for a national hepatitis elimination program to achieve the WHO elimination targets. With the lack donors to support these programs, a new financing mechanism is needed.
Method: A mathematical model was used to estimate the annual funding required to support an elimination program in Uzbekistan. Work Bank data was used to calculate the catastrophic healthcare expenditure (CHE), annual expenditure that will send a family to bankruptcy, for the lowest quartile of the population. It was assumed that 20% of the population could not afford treatment at any price. The number of days required for manufacturing, clearing customs and distribution the product was used to estimate the cash on hand needed to support an elimination program.
Results: In Uzbekistan, the total cost of screening, testing & treatment has to stay below $920 per year, per person. To make the analysis comparable in other countries, a cut off of $250 per year per person was used. Testing & treatment protocols were a key driver of the program cost. We determined that an up-front investment of $1.2 million would support a program to provide free screening for 250,000 people, provide free testing for all HBV+ and HCV+ patients and provide free treatment to 20%. The remaining patients would pay for their treatment at a cost that is below CHE and is 50–80% less than what they are paying today. At the end of the program, the initial investment is recouped to invest in a national program. We are currently conducting a pilot study to demonstrate this novel financing mechanism.
Conclusion: Catalytic investment to fund national programs is a viable option to support hepatitis elimination in LMIC.

SAT337
Meta-analysis: accuracy of the enhanced liver fibrosis (ELF) test in detection of advanced fibrosis or cirrhosis
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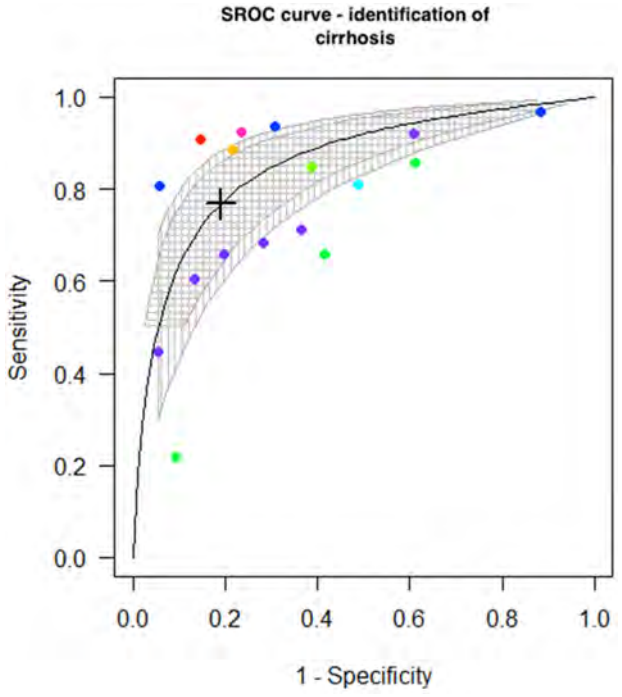
Email: richardparker@nhs.net.

Background and Aims: Background and Aims: non-alcoholic fatty liver disease (NALFD) and alcohol-related liver disease (ArLD) are common diseases but liver-related ill-health occurs in only a fraction of people. However significant liver disease often presents late with cirrhosis. There is therefore considerable interest in the use of non-invasive tests to identify hepatic fibrosis before symptoms occur. We

examined the accuracy of the enhanced liver fibrosis (ELF) test in the identification of hepatic fibrosis.



Method: systematic review of medical literature databases to identify studies reporting on the accuracy of the ELF test in detecting advanced hepatic fibrosis and/or cirrhosis. Random-effect meta-analysis was performed with adjustment for the multiple cut-offs described in the included papers. Results are reported as sensitivity and specificity. Sub-group analysis for advanced fibrosis and cirrhosis was performed. The risk of bias in each study was assessed with the QUADAS-2 tool.

Results: The literature search identified 436 studies of which 13 were suitable for inclusion. These studies included a total of 2255 patients with or at risk of liver disease. The majority of patients had viral hepatitis (hepatitis C, 927 patients; hepatitis B, 462 patients). A further 289 patients had alcohol-related liver disease (ArLD) and 322 patients were included as "chronic liver disease." Six different histological scoring systems were used for histological staging of liver disease. All studies except one recruited patients from secondary care. A range of ELF cut-offs were used, from 5.2 to 11.3. In meta-analysis, ELF detected significant fibrosis with a sensitivity of 74.8 (95%CI 54.1–88.2) and specificity of 74.2% (53.8–87.6), advanced fibrosis with sensitivity of 81.4% (95%CI 75.5%–86.1%) and specificity of 74.9% (67.6%–80.9%) and cirrhosis with sensitivity of ELF was 75.7% (65.9%–83.4%) and specificity 75.9% (66.1%–83.5%). The optimum ELF cut-off for detection of cirrhosis was 10.26.

Conclusion: ELF can accurately detect advanced fibrosis or cirrhosis. However this is based on research predominantly in people with chronic viral hepatitis and in secondary care populations. There are presently few data to support the use of ELF outside of specialist services or on a population level.

SAT338

Risk factors for liver disease cluster geographically: precision public health analysis of a UK city

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Email: richardparker@nhs.net.

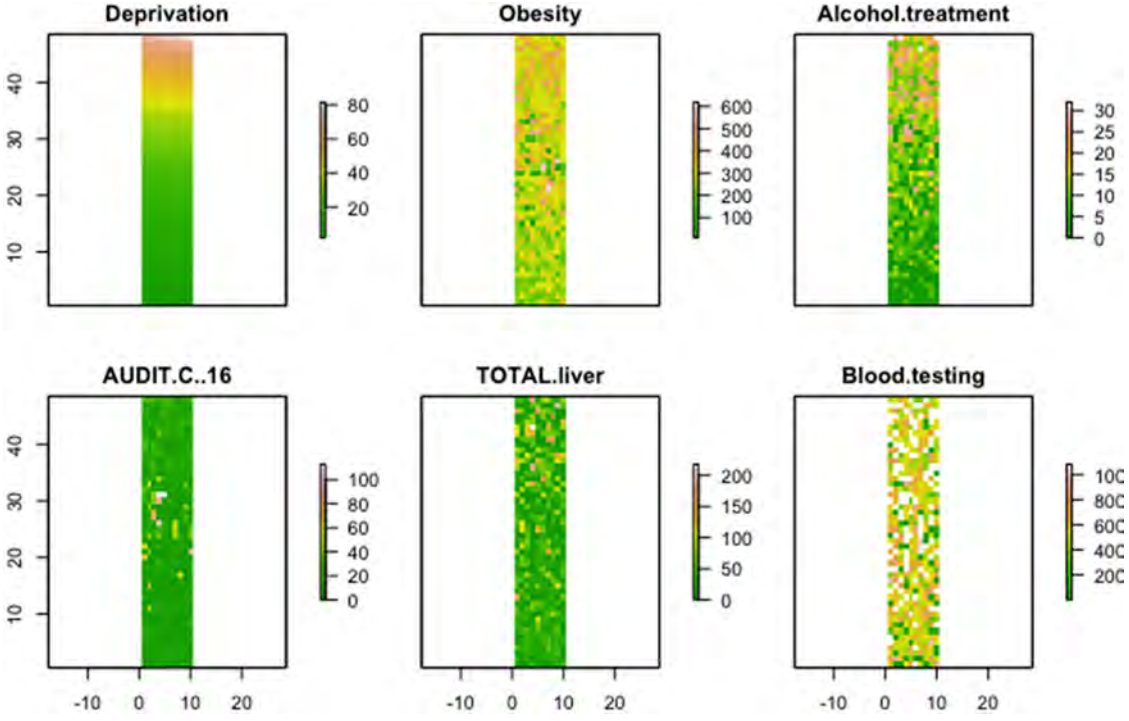

Figure: (abstract: SAT338)

Background and Aims: Liver-related deaths are increasingly common in the UK and are particularly frequent amongst people of working age. Understanding the factors that are associated with liver disease may allow for targeted public health and hepatology interventions to improve health. We investigated liver disease and public health in Leeds, a large city in the north of England.
Method: Leeds is a large city in the north of England with a single hospital provider which also provides laboratory services to primary care. Liver disease was quantified from clinical coding of hospital admissions (number of people admitted to hospital with liver disease). Public health data regarding the prevalence of obesity, diabetes, deprivation and alcohol use from lower output super-areas (LSOA) in Leeds (geographical units of approximately 1500 people) were collated and compared to the incidence of liver disease. Liver blood tests (LBT) were quantified for each LSOA.
Results: Incidence of liver disease was not uniform across Leeds but showed significant variation across LSOA. In multiple linear regression obesity (estimate 0.12, $p < 0.001$), hazardous alcohol use (AUDIT score $\geq$ 16) (estimate 1.14, $p = 0.02$) and severity of deprivation (estimate 0.58, $p < 0.001$) were independent predictors of the incidence of liver disease. These risk factors for liver disease clustered together geographically (figure). The number of LBT from each LSOA was not associated with the incidence of liver disease or the identified risk factors for liver disease.
Conclusion: Deprivation, obesity and alcohol use, measured at a population level are associated with liver disease and tend to occur together. These findings underline the need for robust public-health solutions to reduce the prevalence of liver disease and suggest that case-finding of undiagnosed liver disease could be targeted to areas of high prevalence.

SAT339

Updated estimate for prevalence of chronic hepatitis B among foreign-born persons living in the United States by country of origin

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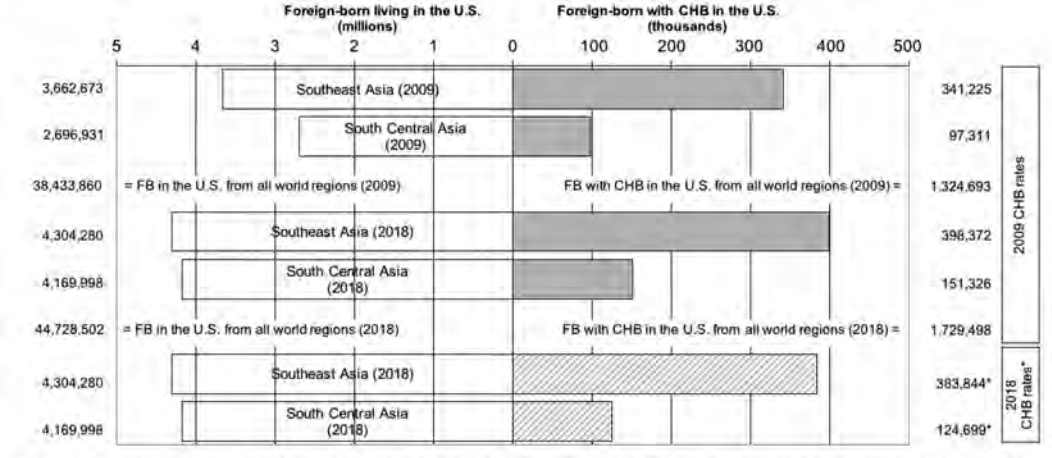
Background and Aims: Foreign-born (FB) persons contribute disproportionately to burden of chronic hepatitis B (CHB) in the United States (U.S.). In 2009, we estimated 1.3 million (M) FB with CHB living in the U.S. based on systematic review and meta-analysis of HBsAg seroprevalence surveys from 102 countries from which FB migrate to the U.S combined with the number of FB in the U.S. from each country using U.S. Census Bureau. Over the past decade, immigration patterns have changed and CHB prevalence likely declined as some countries have implemented hepatitis prevention and vaccination programs. This study reports 1) updated estimates of prevalence of FB with CHB from all regions in the world living in the U.S. in 2018; and 2) updated estimates of FB living with CHB in the U.S. originating from Southeast and South Central Asia (SE and SoCen Asia).
Method: To estimate total FB with CHB in the U.S. in 2018, country-specific CHB rates from the 2009 systematic review and meta-analysis (surveys published 1980 to 2009) were combined with number of FB living in the U.S. in 2018 by country of origin from U.S. Census Bureau. We also updated the systematic review and meta-analysis for SE and SoCen Asia to include reports of HBsAg seroprevalence among emigrants and general in-country populations published from 2009 to 2018. Country-specific pooled CHB rates were calculated including all studies from 1980 to 2018; and the rates combined with number of FB in the U.S. in 2018 by country of birth to estimate the number of FB with CHB from each country in SE and SoCen Asia.
Results: From 2009 to 2018, overall FB population in the U.S. increased by 16% (38.4M to 44.7M) (Figure). Based on the change in FB population alone—and assuming no change in CHB rates from 2009 estimates—total number of FB with CHB in the U.S. would have increased by 31% (from 1.3 M to 1.7 M); and the number of FB with CHB from SE and SoCen Asia by 18% and 55%, respectively. Accounting for both increased FB population and revised CHB rates from the updated systematic review, FB with CHB in the U.S. from SE and SoCen Asia are estimated to have increased by 13% and 28%, respectively.
Conclusion: Interim analysis of this updated systematic review suggests continued immigration has increased the number of FB living with CHB in the U.S. despite likely declines in CHB prevalence rates in many countries of origin. CHB prevalence rates in all 102 countries of origin included in the 2009 analysis will be presented.

Figure 1. FB Populations living in the U.S. and prevalence of FB with CHB in the U.S. from random effects meta-analysis by world region of origin.



Sources: U.S. Census Bureau (2010), *2009 American Community Survey*; U.S. Census Bureau (2019), *2018 American Community Survey*; Kowdley, K. V., Wang, C. C., Welch, S. , Roberts, H. and Brosgart, C. L. (2012), Prevalence of chronic hepatitis B among foreign-born persons living in the United States by country of origin. *Hepatology*, 56: 422-433. doi:10.1002/hep.24804.
**FB with CHB by region calculated using FB population by country and country-specific midrange random effects CHB rates using all surveys published 1980 to Oct 2018.*

Figure: (abstract: SAT339)

SAT340

Improving access to care for serologically positive hepatitis C blood donors in private sector

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Background and Aims: 6.8% of adult Pakistani population is reported to be hepatitis C (HCV) seropositive but only 14% are aware of their infection status. Usually, HCV seropositivity is an incidental finding during blood donation process. Due to several factors such as lack of integration between blood centers and clinical services and high cost of care, identified seropositive donors are left to search for treatment on their own, posing major obstacles in patient's journey to access care. In November 2018, we initiated active tracking and linkage to care of seropositive blood donors, through integration of blood bank and HCV services, both of which were available at The Indus Hospital in Karachi, Pakistan.
Method: Standard operating procedures (SOPs) were established to ensure seamless communication between both teams. Blood center recorded donor personal details and demographics, counselled donors regarding test results and ensured linkage with the HCV clinic. The HCV program team tracked them through each step of the care cascade i.e. from diagnostic testing to sustained virological response (SVR 12) response. All eligible were treated with Sofosbuvir and Daclatasvir based treatment regimens. All services were offered free of cost.

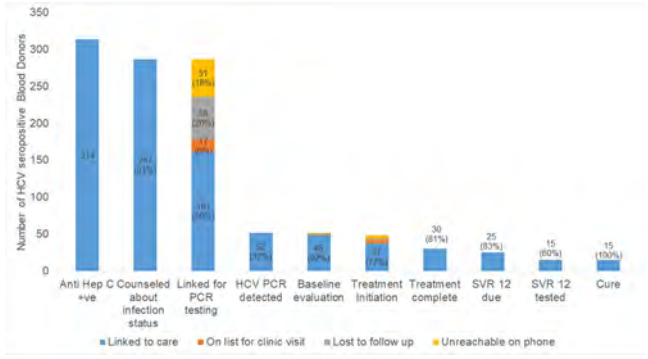

Figure: Linkage to care for PCR testing and treatment uptake

Results: From July 1, 2018 to September 30, 2019, 28,173 donors were registered in blood bank database and majority of whom were male. Blood donation camps were organised in factories, mosques and schools. 314 (1.1%) donors were seropositive for HCV: 307 (98%) were males; mean age was 29 years (range : 17–51 years). 287 (91%) donors were informed about their blood screening results, 8% could not be contacted due to wrong phone number (unreachable) 2% wanted to seek care outside Indus Hospital. Of 287 donors counselled, 161 (56%) have been tested for Polymerase Chain Reaction (PCR), 17 (6%) are scheduled for clinic visit, whereas 51 (18%) remain unreachable and 58 (20%) have not returned to the clinic despite being connected via phone (lost to follow up). Of those PCR tested, 52 (32%) were found to have active infection: of these 48 (92%) returned to the clinic for further evaluation. 37 (77%) were started on treatment and 5 (10%) are scheduled to return to clinic. 30 (81%) patients have completed treatment. Of 25 (83%) due for SVR 12 testing, only 15 (60%) are tested so far and all achieved cure.
Conclusion: Integration of blood bank with clinical care services is possible through the use of minimal resources. There is a dire need for establishing a central database for sharing of information across various health care services including blood centers to improve access to care for hepatitis C.

SAT341

Comparison of costs of different HCV screening and linkage to care interventions across Europe

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Background and Aims: HCV is a blood borne virus mainly transmitted through injecting drug use in European settings, with long term consequences including liver disease and hepatocellular carcinoma. This study aims to compare the costs per person screened, diagnosed/identified, and linked to care for various pilot interventions undertaken as part of the HepCare Europe programme.
Method: Four interventions were costed: 1. Nurse liaison for GP prescribers of OST in Dublin (HepLink Dublin); 2. Nurse led mobile outreach in London targeting homeless populations and people who inject drugs, with peer support for linkage to HCV treatment in hospital (HepFriend London); 3. Mass opt-out screening in a Dublin prison with a peer based awareness program (HepCheck Dublin); and 4. Screening and linkage to care in targeted high-risk settings in Bucharest (HepCare Bucharest).
For each site, intervention costs were collected by interview with intervention staff using a top down approach, including staff costs, resource use and HCV test costs. Setup costs were annualised over 5 years. The cost (in €) per person screened, diagnosed and linked to care was calculated for each intervention. Costs and patients screened, diagnosed, and linked to care for HepFriend London were taken from the middle year of the intervention.
Results: The costs per year were €64,806, €112,093, €81,505, and €56,647 for HepLink Dublin, HepFriend London, HepCheck Dublin, and HepCare Bucharest, respectively. The cost per patient outcome were impacted by the size of the target population reached and the prevalence of HCV in each setting. The HepFriend London intervention also had a peer support component helping patients to attend hospital appointments and adhere to treatment which cost an additional €775 per patient treated (n = 44).

	Number of outcomes and unit cost per each outcome					
	Screened		Diagnosed/ identified		Linked to care	
Intervention	N	Unit Cost	N	Unit Cost	N	Unit Cost
HepLink Dublin	102	€635	57	€1137	43	€1507
HepFriend London	273	£248	121	£558	110	£1171
HepCheck Dublin	419	€194	50	€1630	40	€2038
HepCare Bucharest	525	€108	230	€246	154	€367

Conclusion: Within HepCare Europe, the unit costs per person differed by 6-fold between the highest (HepLink Dublin) and lowest (HepCare Bucharest) cost interventions. This highlights that the implementation of similar interventions in different settings within Europe can have very different costs. A crucial next step will be to evaluate the impact of these interventions on patient outcomes.

SAT342

High patient acceptability for a hepatitis C mobile outreach service targeting 'vulnerable' homeless communities - an important component for elimination?

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Background and Aims: Given the HCV elimination agenda, finding and treating 'seldom heard' communities such as the homeless is critical. Such populations do not interface well with traditional models of care. In 2018, King's College Hospital, in collaboration with The Hepatitis C Trust, commissioned a mobile clinic to screen and treat homeless people in Lambeth, Lewisham and Southwark for HCV. The 'HCV Mobile Outreach Service' includes point-of-care finger prick HCV screening (InTec anti-HCV antibody) and confirmatory testing (Cepheid finger GeneXpert prick HCV RNA), non-invasive liver assessment by Fibroscan (Echosens), a multidisciplinary medical team (including peer) and needle and syringe programme provision. The aim of this study was to measure the patients' acceptability of the service model (overall service, finger prick testing and peer).

Method: Patient acceptability was assessed using a theoretical framework of acceptability (TFA) survey (Sekhon et al, 2017) which considers cognitive and emotional responses to an intervention. It is formed of seven distinct constructs (affective attitude, burden, ethicality, perceived effectiveness, intervention coherence, self–efficacy and opportunity cost). Each construct is measured by a 5-point Likert scale. Question 1 (Q1) indicates overall performance and either a score (out of 35) for Q2-8 or a composite be calculated. At Q6, patients were asked to elaborate further about their views allowing qualitative insight. A paper survey was administered to patients using a purposive sampling strategy. Consent was received verbally.

Results: Demographics - 35 patients (60% Male, 40% Female), Intravenous drug use (34% current, 26% past use, 40% never), HCV status (11% past infection, 40% current infection, 45% never infected). The results suggest patient acceptability for all components were high. Few chose to elaborate further, (response rates: overall service (37%), finger prick testing (37%) and Peer Navigator (20%)). Most comments were positive describing the benefit of not having to attend appointments at the hospital and a preference for engaging with a Peer. Although patients found the finger prick testing less acceptable than other components of the service, feedback suggests it is more acceptable than venepuncture.

Distribution of the patients' TFA score and composite mean.

Conclusion: The HCV Mobile Outreach Service is considered a highly acceptable intervention by this community and could contribute to HCV elimination efforts, linkage to other facets of care is currently being evaluated.

SAT343

Health and economic burden due to alcohol related liver diseases in New Delhi, India: a Markov probabilistic modelling approach

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Background and Aims: Liver diseases account for nearly one-fifth of all the deaths attributable to alcohol. The current study carefully examines the health and economic burden due to Alcohol related liver diseases (ALD) for the Union territory of New Delhi, India from 1st March 2017 to 28th February 2018.

Method: The current study employs a Markov Probabilistic Modelling approach using the following health states; No ALD, Alcoholic steatosis, Alcoholic steatohepatitis, Alcoholic cirrhosis and death. The model assumed that health transitions and deaths related to liver diseases and other causes occurred uniformly throughout the year. The health impact due to ALD was estimated through 1) Disability adjusted life years (DALYs) and Years of life lost (YLL) due to liver diseases, and, 2) total deaths due to ALD. The economic burden to the health system was assessed for two scenarios; 1) assuming the current health seeking preferences and 2) if all diseased individuals sought care in public health systems. Sensitivity analysis was done by 10000 Monto Carlo simulations and 90% non-parametric confidence intervals (90% CI) were estimated.

Results: The total number of estimated deaths due to ALD was 10,625. The DALYs due to ALD was 0.314 million life years which includes 0.225 million years of premature life lost (YLL) and 0.088 million life years lost due to disability (YLD). The total cost of treating ALD if patients sought care based on current preferences was estimated to be 1.64 billion USD [Table 1].

Table 1: Health and economic burden due to ALD in Delhi

Characteristic	Value (90% CI)
Economic cost based on current preferences (in billions)	
Total cost to the public health care system for treating ALD in USD	0.13 (0.10–0.17)
Total out of pocket expenditure for treatment in USD	1.51 (1.05–1.98)
Total cost for treatment of ALD in USD	1.64 (1.17–2.13)
Economic costs if all patients seek care in public health systems for ALD (in billions)	
Total cost to the public health care system for treating ALD in USD	0.42 (0.34–0.55)
Total out of pocket expenditure for treatment in USD	0.56 (0.38–0.78)
Total cost for treatment of ALD in USD	0.98 (0.74–1.30)

Conclusion: Nearly 10,600 deaths and 0.314 million years of DALY lost and an estimated expense for care amounting to USD 1.64 billion is estimated to be due to ALD in New Delhi in one year. It would be prudent to initiate social engineering and preventive strategies to lessen the growing burden of ALD in India.

Table: (abstract: SAT342) Distribution of the patients' TFA score and composite mean.

	Overall acceptability mean (Q1)	SD	Median	IQR (Interquartile range) 0.25	IQR (Interquartile range) 0.75	Composite score mean (Q2-Q8)	SD	Median	IQR (Interquartile range) 0.25	IQR (Interquartile range) 0.75
Overall service	4.8	0.43	5	5.00	5.00	4.5	0.39	4	4.3	4.7
Finger prick blood testing	4.4	0.73	4	4.00	5.00	4.2	0.54	4	3.9	4.5
Peer	4.7	0.58	5	4.50	5.00	4.4	0.40	4	4.1	4.7

SAT344

No restrictions should be placed on future treatment for patients who discontinue DAAs on their first or second attempt. A real world experience from the TraP HepC initiative in Iceland

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Background and Aims: To achieve elimination of hepatitis C virus (HCV) as a major health threat, the World Health Organization (WHO) has set treatment service coverage targets of 90% diagnosis and treatment of 80% of eligible patients by the year 2030. The TraP HepC program in Iceland aims to eliminate domestic transmission of HCV by offering treatment to all known cases, focusing on those most likely to transmit. To reach the WHO targets, strategies are needed for those patients who discontinue or otherwise fail treatment.

Method: Starting in 01/2016 all HCV positive patients are offered direct acting antivirals (DAAs). People who inject drugs (PWID), prisoners, and patients with advanced liver disease are prioritized. Patients who discontinue treatment and remain viraemic as well as reinfected patients are reengaged in care and offered retreatment. Here we analyzed engagement in care and sustained virologic response rates at ≥12 weeks post treatment (SVR≥12) for all individuals who commenced treatment from Jan 2016 to Jan 2019.

Results: Treatment was initiated for 718 individuals, 98% of the eligible (HCV PCR positive) patient population of whom 703 patients (98%) gave consent for study participation. Mean age was 44 years (IQR 34–54), males 474 (67%). The most common route of infection was injection drug use (IDU, 85%), 33% reported recent (within 6 months) IDU; 7% were homeless, and 5% incarcerated. Stimulants were preferred by 85% of PWID, opioids by 13%. Overall, 9% were on medication assisted therapy for opioid use disorder.

Of 703 who initiated treatment, 650 (92.5%) completed treatment with PCR results ≥12 weeks available for 632. A total of 603 (95%) were PCR negative and 29 positive (12 reinfections, 12 relapses, data pending for 5). Of 53 who discontinued treatment, SVR>12 data are available for 47 of whom 25 (53%) are PCR negative and 22 positive. Overall, if patients with no SVR>12 results are counted as failures, the cure rate for first DAA treatment was 89%.

During the period, a second treatment course was initiated in 70 individuals, 66 completed treatment, and SVR12 results are available for 63. A total of 60 (95%) were cured and 3 PCR positive. Data is missing or pending for two, one died before reaching SVR≥12. Of the 4 (6%) patients who discontinued treatment during round 2, three remained positive and one achieved SVR≥12.

In total 7 patients received a third treatment round, of whom 6 completed treatment. All 6 completers reached SVR≥12, but the remaining patient who discontinued had persistent viraemia.

Conclusion: Patients who discontinue treatment on the first and second attempt are highly likely to complete therapy if they reengage in care for their second or third attempt. Their cure rates are comparable to those who complete the course on their first attempt. No restrictions for future treatment should be placed on patients who discontinue DAAs on their first or second attempt.

SAT345

National survey among people who use drugs (PWUD) on opioid substitution treatment (OST) on their knowledge of hepatitis C virus (HCV) infection and barriers for treatment in Bulgaria

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Background and Aims: OST in Bulgaria is provided only in OST centers (OSTC). Currently, there are 30 OSTC (5 state and 25 private) in 16 cities in the country with 3247 clients. HCV seroprevalence among PWUD is 68%. OST is not a contraindication for HCV treatment, however treatment rates among HCV – positive OST patients remain low. Only people with health insurance can receive HCV antiviral treatment. No other funding for treatment exists. The aim of the study was to investigate the knowledge of HCV infection and the barriers for treatment among PWUD on OST in Bulgaria.

Method: A survey with multiple choice structured questionnaire (16 questions covering demography, epidemiology of drug use, HCV testing and treatment, barriers to treatment) was offered in all OSTC in Bulgaria. Questionnaires were anonymous, filled by the patients. Statistical analyses were done by Kolmogorov-Smirnov, Chi-Square, Mann-Whitney and Kruskal-Wallis tests.

Results: From 01 May to 31 October 2019 1907 patients (58,7%) from 21 OSTC (70%) in 15 cities participated in the survey. 1495 males/412 females, mean age 38,26 ± 5,78years/36,86 ± 6,85years ($p < 0,001$) completed survey. Mean duration of drug use in males/females −13,19 ± 6,11years/12,16 ± 6,47years ($p < 0,001$). HCV seroprevalence was 61,2%. 95,6% of PWUD have ever been tested for HCV Ab. There was significant correlation between HCV Ab testing and intravenous drug use (IVDUs) ($p < 0,001$): IVDUs were reported from 9,9% people in ≤3 months, 7,7% in ≤6 months, 8,9% in ≤12 months, 60,7% in ≥12

months ago, HCV Ab testing was reported from 15,2% people in ≤3 months, 17,5% in ≤6 months, 15,5% in ≤12 months, 47,4% in ≥12 months ago. Antiviral treatment was conducted in 18,6% of infected individuals, 67,3% had IFN treatment and 32,7% had DAAs, 26,7% were in state and 73,3% in private OSTC. 45,4% from state and 30,9% from private OSTC had no health insurance. According to PWUD main barriers for treatment were: 27,4% lack of health insurance, 19,1% no treatment were offered, 13,0% didn't know were to go for treatment, 13,5% treatment was not a priority for them, 11,5% thought, that treatment had too many side effects, 10,8% thought, that HCV can't be cured, 4,7% didn't want to be treated.

Conclusion: Low treatment rates among PWUD on OST in Bulgaria are related to lack of health insurance, poor linkage to care and low awareness about new treatment options, although there was gut knowledge about IVDUs as a risk behavior for HCV infection acquisition. Join efforts from the government and the stakeholders are needed in order barriers for treatment to be overcome.

SAT346

Demonstration of the feasibility of two innovative models of HCV testing and treatment in two unique populations in Punjab and Delhi, India-head- start project, India

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Background and Aims: It is estimated that 33 million people with hepatitis C Virus (HCV) live in Asia and approximately 80 million may be chronically infected globally.[1] Despite significant advances in testing technologies, simplified algorithms and effective treatment options, four out of five people infected remain undiagnosed. In 2018, the Foundation for Innovative New Diagnostics (FIND) in collaboration with Ministries of Health (MOH) and local partners initiated the Unitaid-funded Hepatitis C Elimination through Access to Diagnostics (HEAD-Start) across two states in India (Delhi and Punjab) to demonstrate innovative models of HCV care to inform scale up nationally and globally.

Method: Target populations and settings included the general population in polyclinics, district hospitals and screening camps (Delhi) and PLHIV in ART clinics (Punjab, India). All projects employed the use of rapid diagnostic tests (RDT) for HCV screening in decentralised settings. HCV seropositive patients received confirmatory testing using a centralized laboratory-based assay in Delhi, at GeneXpert testing hubs in Punjab. We describe preliminary findings for the retention of patients in the HCV cascade.

Results: Between 23 Jan to 7 Oct 2019 in Delhi, 38,864 patients were screened at 5 Districts Hospitals (22,756), 15 Polyclinics (10,334) and 30 screening camps (5774), of whom 2.2% (837) HCV seropositive. 87% (726) received HCV RNA testing and 77% of the 626 patients confirmed positive were initiated on treatment (483). To date, 32% (155) have completed treatment, 31.6% (49) received SVR-12 testing and 94% (46) achieved cure. In Punjab (22 Oct 18 to 30 Sep 19), 81% (25, 462) of all PLHIV attending (31,613) at all state-wide ART clinics (n = 13) have been screened, with 21% (5354) found HCV seropositive, 91% (4868) received HCV RNA testing and 35% of the 4088 patients confirmed positive, have initiated treatment (1422). To date 28% (397) patients have completed treatment, 40% (160) have had SVR 12 testing and 86% (137) have achieved cure.

Conclusion: In general, the least complicated and most decentralised models of HCV care demonstrated better retention in the care cascade. However, each setting is unique with different populations, settings and policies that requires careful consideration when considering the most appropriate models of HCV care for scale up.

Reference

1. Gower E, Estes C, Blach S, et al. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol.* 2014;61(1 Suppl):S45–57.

SAT347

Barking up the wrong tree: why universal hepatitis C virus screening is not enough for its elimination in the US

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Background and Aims: Hepatitis C virus (HCV) screening is a crucial step in HCV elimination. Currently, the United States Preventive Services Task Force proposes universal HCV screening of American adults (ages 18–79), expanding on the prior risk- and age-based recommendations including testing individuals born between 1945 and 1965 (henceforth Baby Boomer Birth Cohort, BBBC). With a hypothesis that the burden of HCV infection is larger in parts of the US population with poor access to healthcare, we compare the prevalence and characteristics of HCV infection in Americans with and without health insurance coverage.

Method: Data from all adult examinees participating in the National Health and Nutrition Examination Survey (NHANES) in 2013–2016 were analysed for demographic and laboratory characteristics as well as insurance status. Subjects were divided into BBBC and post-BBBC (born in 1966 or later). HCV infection was defined by detectable HCV RNA in the serum. Appropriate statistical techniques were used to account for the stratified sampling design of NHANES.

Table 1: Prevalence of HCV infection in NHANES 2013–2016 participants (weighted data)

Prevalence	Overall	Insured	Uninsured	p-value
BBBC (born in 1945–1965)				
Positive anti-HCV (%)	3.31	2.97	6.20	0.015
Positive HCV RNA (%)	1.79	1.49	4.36	0.002
Post BBBC (born after 1965)				
Positive anti-HCV (%)	1.12	0.87	1.98	0.012
Positive HCV RNA (%)	0.50	0.23	1.40	0.002

Results: In the survey, data were complete in 8,640 examinees, projecting to 186 million American adults. Overall, 17.8% lacked insurance coverage. In Table 1, HCV prevalence was higher in BBBC (1.79%) than in post-BBBC (0.50%). In both age groups, HCV was significantly more common among uninsured individuals than insured. The discrepancy was larger in the post-BBBC: HCV infection was 6 times more common in the uninsured than in the insured (1.40% versus 0.23%), compared to 3 times in BBBC. Importantly, the yield of HCV RNA testing among anti-HCV+ subjects differed by

insurance status and age group. In the uninsured, 70% of anti-HCV+ subjects had HCV infection regardless of age. Lower proportions had HCV infection in the insured: 50% in BBBC and 26% in post-BBBC. Among HCV-infected subjects, 63% had insurance. Other than age (those without insurance were younger, 46 versus 56 years, $p < 0.01$), there was no significant difference in individual characteristics by insurance status including liver biochemistry, FIB-4 and awareness of HCV status.

Conclusion: When health insurance is used as a surrogate for access to healthcare, HCV burden and the yield of screening is inversely correlated with healthcare access. In order to make a meaningful progress in HCV elimination, strategies to uncover HCV in individuals without regular access to healthcare need to be pursued.

SAT348

From emergency department automated hepatitis B & C screening to care and cure in a primary care practice

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Background and Aims: Globally, 20% of people with hepatitis C (HCV) and 9% of those with hepatitis B (HBV) are aware of their infection. In the US, up to 2.2 million are estimated to have HBV and 2.4 million have HCV. Scale-up of screening and care is needed to achieve hepatitis elimination by 2030. We aimed to create a viral hepatitis (VH) screening protocol in the Emergency Department (ED) of a community hospital with about 100,000 visits a year with linkage to a primary care practice to provide hepatitis care.

Method: An automated algorithm was set up in the ED utilizing Cerner electronic health record (EHR). Eligibility criteria for HCV testing is by year of birth (1945–1965) and for HBV is a country of origin endemic for HBV. If a patient is eligible and bloodwork is ordered, a Hepatitis C antibody (HCV Ab) with reflex to HCV RNA or a Hepatitis B surface antigen (HBsAg) order automatically fires and is added to lab orders. EHR alerts notify nursing of patient eligibility and reactive results. Patient navigators (PN) receive notification via encrypted text message in real-time and work with the patient to arrange VH evaluation. PNs directly schedule patients to an outpatient primary care practice and are integrated into the team of 4 internists and a pharmacist trained in VH care.

Results: From March 2018–August 2019, a total of 22,780 VH screening tests were done, with 12,473 for HCV and 10,307 for HBV. There were 137 found to have current HCV infection (1.1%) and 131 HBV infection (1.2%). Linkage to first medical appointment rates were 87.8% for HBV and 88.4% for HCV. There were 38 HCV patients seen at the primary care practice, with 27 initiating HCV therapy and thus far, 23 (77.8%) have undetectable HCV RNA at week 4, and 16 (42.1%) have confirmed cure at 12 weeks post-therapy with others pending. None of those initiating therapy have fallen out of care. The top 3 countries of origins for the HBV infected patients are Haiti, China and Nigeria.

Conclusion: Automated HBV and HCV screening in the ED can significantly scale up screening and target high risk populations. The HCV prevalence rate was similar to the overall US population, but for HBV, it was 3 times the prevalence rate in the US (0.4%). Country of origin is an effective way to identify those at risk for HBV and is more specific than race. Models of care utilizing frontline providers are important for expanding the reach of critical hepatitis services in the quest for hepatitis elimination.

SAT349

Prevention of liver diseases through universal coverage with hepatitis B vaccination in India

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Background and Aims: Hepatitis B is a significant public health problem in India. The current prevalence is in the range of 2–8% in the general population. Mother to Child Transmission is the most important route of HBV transmission. HBV is reported to be responsible for 50% of the cases of chronic hepatitis and 35–60% of the cases of cirrhosis of liver. It is estimated that about 60% of the patients with hepatocellular carcinoma are HBV marker positive. There are approximately 50 million HBV infected subjects.

Immunization remains the most effective way to control the spread of HBV infection hence universal vaccination coverage of all infants is being undertaken under the centrally sponsored National Immunisation program. All infants are to be given HBV vaccination at 0 day, 6,10 and 14 weeks.

Method: The data collected in the National Family Health Survey-4 (NFHS-4) conducted in 2015–16 which covered 199,899 children in the age group of 12–59 months in 36 states of country was utilized for present study.

Results: It is found that overall 62.7% of all children received 3 rd dose of HBV. There wa no significant difference for gender or urban vs rural areas for the HBV coverage. Children of first birth order are much more likely to receive HBV than children of birth order 6 or more (66.9% versus 45.3%). The Vaccination coverage increased with the increased in the mother's schooling (no schooling 53% vs 69% 12 yrs or more schooling). Sikh children received HBV vaccinations than Muslim (89% vs 56.6%). Vaccination coverage increased with increasing wealth status; 68.6 percent of children from households in the highest wealth quintile received HBV vaccinations, compared with 55.2 percent of children from households in the lowest wealth quintile. The children from scheduled caste communities communities had loewest coverage as compared to other tribes (55.2 vs 65.1%). Coverage of HBV varied considerably by state and union territory. The coverage is highest in Punjab (91%) and lowest in Nagaland (45%). The other determinants in the HBV coverage of children will be discussed.

Conclusion: There is a need of developing statewise strategies to improve coverage of HBV vaccination based on the determinants which are leading to low coverage of HBV vaccine.

SAT350

Deleterious impact of advanced non-alcoholic steatohepatitis on multiple patient-relevant outcomes: an international, cross-sectional, real-world study

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Background and Aims: Nonalcoholic steatohepatitis (NASH) is often described as an asymptomatic disease. NASH patients with advanced fibrosis (AF; NASH CRN Stage ≥3) are at higher risk of developing adverse health outcomes vs patients with early fibrosis (EF; NASH CRN Stage ≤2). However, data comparing patient-relevant outcomes among patients with AF and EF are lacking. This analysis aimed to evaluate the impact of AF on patients' lives by comparing multiple patient-relevant outcomes among those with AF and EF.

Method: Data were derived from the 2018/19 Adelphi NASH Disease Specific Programme, a real-world, cross-sectional chart review in the US and UK. Physicians completed questionnaires describing 5–6 consecutive NASH patients with any fibrosis stage, then 2 patients with F3–F4 fibrosis. Patients were categorised as AF or EF based on

most recent FibroScan (AF ≥9.6 kPa; EF <7.9 kPa) or FIB-4 result (AF ≥2.67; EF <1.30) and completed voluntary assessments of sleep impairment (Jenkins Sleep Evaluation Questionnaire [JSEQ]; 1–no to 20–constant disturbance); quality of life (Chronic Liver Disease Questionnaire [CLDQ-NASH]; 1–most to 7–least impairment); health status (EQ-5D-5L; VAS); Work Productivity and Activity Impairment (WPAI; % impairment) and impact on activities of daily living with NASH (ADL; 0–not to 3–greatly affected). AF and EF patients were compared using multivariate regression adjusting for age, sex, smoking, education, BMI, type 2 diabetes, and Charlson Comorbidity Index.

Results: 162 physicians provided data on 1245 NASH patients. 696 patients met the criteria for AF or EF and 212 completed the patient survey. Mean age was 53 years and 58% were male. AF patients reported significantly higher impact on patient-relevant outcomes compared to EF patients in multivariate analyses (Table; all $p < 0.05$). Consistent trends were observed across the US and UK.

	AF (n = 157)	EF (n = 55)
JSEQ (score)	5.4	1.7
WPAI (% activity impairment)	32	12
EQ-5D-5L (utility score)	0.86	0.94
EQ-5D-VAS (%)	74.7	83.4
Impact		
Social life	0.8	0.2
Motivation	1.0	0.3
Freedom to eat/drink	1.5	0.6
Feelings about future	1.3	0.6
	AF (n = 113)	**EF (n = 50)**
CLDQ-NASH (score)		
Total score	5.3	6.1
Abdominal	5.1	6.0
Activity	5.2	6.0
Emotion	5.3	6.2
Fatigue	4.9	5.7
Systemic	5.6	6.2
Worry	5.4	6.2

Conclusion: In a real-world setting, AF NASH patients report significant impairment on a range of patient-relevant outcomes vs EF patients. These findings contradict the widely held view that NASH is an asymptomatic disease, highlighting fibrosis severity as a key driver of patient burden.

SAT351

Factors associated with failure to link people who inject drugs to HCV care and treatment: results from a community-based seek-test-treat program in Athens, Greece (ARISTOTLE HCV-HIV)

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Background and Aims: Eighty per cent of people who inject drugs (PWID) in Athens, Greece, are HCV infected and linkage to HCV care remains at low levels in this population. A community-based program is implemented in Athens since April 2018 with the aim to screen for HCV and improve access to care and treatment among PWID (ARISTOTLE HCV-HIV). Aim of this analysis is to identify factors associated with failure to link PWID to HCV care and treatment.

Method: ARISTOTLE HCV-HIV is a "seek-test-treat" program where PWID are recruited using chain-referral sampling with monetary incentives. Participation includes interviewing, blood testing, evaluation of liver fibrosis and counseling. All services are provided on site. There is a network of collaborating hepatologists and infectious diseases and a peer-navigator accompanies patients to the clinics for their first appointment. In the first 5 months of recruitment, fibrosis-based treatment restrictions applied. We present data from the first recruitment round (April 2018-January 2019); information on linkage to care (first appointment with the physician) and treatment initiation were updated in September 2019. Logistic regression was used to obtain adjusted odds ratios (aOR) and 95% confidence intervals (95% CI) for the impact of sociodemographic characteristics, injection behaviours and access to harm reduction programs on the two outcomes (linkage to care and treatment initiation).

Results: Of 1,365 participants, 395 had HCV monoinfection and were eligible for treatment with DAAs during the period of HCV diagnosis; 13.7% were women, 77.5% were current users, 24.8% homeless, 14.2% migrants and 72.9% not linked to opioid substitution treatment programs. During the program, 47.6% (188/395) were linked to HCV care and 42.2% (167/395) initiated treatment with DAAs. Factors associated with higher risk of not being linked to care (aOR [95% CI]) were homelessness (homeless vs. not homeless: 2.6 [1.6, 4.4], $p < 0.001$) and being migrant (non-Greek vs Greek origin: 3.7 [1.8, 7.5], $p < 0.001$). An additional factor associated with higher risk of not initiating treatment was gender (aOR (95% CI) for women vs men: 2.1 (3.7 (95% CI: 1.1, 4.0), $p = 0.022$).

Conclusion: The program achieved satisfactory linkage to care rates in a population of current PWID. However, additional efforts are needed for migrants and homeless PWID. Tailored interventions and empowerment in necessary to increase treatment uptake among women PWID.

SAT352

Clinical and economic consequences of antiviral treatment for hepatitis C chronic infection in Europe: analysis of England, Italy, Romania and Spain data

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Background and Aims: The development of country-specific models enables evaluation of HCV therapy impact in the liver disease burden and economic consequences according to the treatment eligibility criteria over time across countries. In this study, we built country-specific models for Italy, Spain, United Kingdom and Romania to assess, by country, the clinical and economic impact of antiviral therapy and to predict for each country the necessary time to recover the initial investment for treatment according to differences in the epidemiology and treatment access over time.
Method: A multistate, 20-year time horizon HCV liver disease progression Markov model was developed considering specific DAA treatment eligibility in each of the countries during the years 2015 and 2018. Data stratifications for the disease states, genotypes were retrieved from real world data sources at national level. The period of time required to recover the NHS investment in DAA treatment was calculated on the basis of the cost saved by the avoided clinical events estimated. All data were standardized for 1000 patients treated.
Results: For 1000 standardized patients treated during 2015/16, the estimated number of avoided HCV-clinical related events (HCC, Decompensated cirrhosis, liver related death reported as single events) for 1000 patients during 20 years following viral eradication was: 1136 in Italy; 1310 in Romania; 1040 in Spain and 1134 in England. For 1000 standardized patients, treated during 2017/18, our model estimated: 565, 908, 505 and 546 clinical events to be avoided during 20 years after viral eradication in Italy, Spain and England respectively. The potential clinical outcomes reduction on time, standardized for 1000 of patients treated from 2015–2018, reflect important cost savings over 20 years reported to be as follows: reduction of € 52 million in Italy, of € 57 million in Romania, 194 million in Spain and of 48 million in England. The investment of National Health System for DAA drugs is estimated to be recovered in 5.6 years in Italy, 6.5 years in Romania, 4.6 years in Spain and 7.5 years in England.

Table: Avoided events and costs by country

Country	Year	Return of Investment years	Avoided cases after 20 years	Increasing costs after 20 years (€ million)
Italy	2015/2016	7.5	−1136	−€ 19,670,908
	2017/2018	4.5	−565	−€ 69,441,123
	Overall	5.6	−832	−€ 52,205,897
Romania	2015/2016	5.9	−1310	−€ 57,143,054
	2017/2018	4.6	−908	−€ 73,434,132
	Overall	6.5	−1040	−€ 57,433,459
Spain	2015/2016	5.0	−892	−€ 205,276,612
	2017/2018	3.9	−505	−€ 169,839,112
	Overall	4.6	−701	−€ 194,165,218
England	2015/2016	6.6	−1134	−€ 41,258,934
	2017/2018	4.5	−546	−€ 88,165,777
	Overall	7.5	−577	−€ 48,897,213

Conclusion: The use of DAA for chronic HCV infection is translated not only in significant clinical benefits but also in substantial cost savings over 20 years period.

SAT353

The head-start project: introduction of rapid diagnostic tests for hepatitis C screening in primary healthcare sites as a first step towards decentralizing hepatitis C care in Malaysia

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Background and Aims: Malaysia is an upper-middle income country of 32 million people and is estimated to have a hepatitis C virus (HCV) general prevalence of 2.5%. Implementation of the HCV national strategic plan was fraught with obstacles including restrictive drug access policies and a complex and centralized screening algorithm (2 enzyme immunoassay and 1 core antigen). The Foundation for Innovative New Diagnostics collaborated with the Ministry of Health and the Drugs for Neglected Diseases *initiative* on a Unitaid-funded Hepatitis C Elimination through Access to Diagnostics (HEAD-Start) project to introduce decentralised HCV screening at the primary health care (PHC) level. Here, we describe preliminary findings from the study.
Method: The project incorporates a partially decentralised model of HCV care. HCV rapid diagnostic tests (RDTs) were introduced at 25 PHC sites offering methadone maintenance therapy services. Participants, aged 18 to 70 years and at risk of HCV infection, were enrolled and screened. Seropositive patients were subsequently referred to one of the 5 tertiary hospitals for confirmatory testing via a centralized laboratory.
Results: 15,148 participants were screened using HCV RDT, of whom 20% had piercings, 17% had a prior invasive medical procedure, 13% were injecting drug users, 10% were intranasal drug users, 8% were previously incarcerated, 7% were people living with HIV, 5% were men who had sex with men and 5% had chronic liver disease. Of those screened, 13.4% were HCV seropositive, of whom 61.1% received RNA confirmatory testing and 63.5% of those confirmed RNA-positive received pre-treatment assessments. The mean time between RDT screening and RNA sample collection at hospitals was 17 days; between RNA sample collection and testing at a centralised lab, 13 days; between sample collection and results returned to patients and between results returned to patients and treatment referral were both 41 days each.
Conclusion: Introduction of HCV RDTs at PHC sites has helped to increase screening coverage with positive case findings and has catalysed national uptake of a simplified HCV screening algorithm. Further optimisation and scale-up of this HCV model of care will involve a fully decentralised care pathway at the PHC sites including RNA sample collection for seropositive patients and treatment of uncomplicated cases to improve retention in the care cascade and decrease the turn-around time for patients to receive treatment.

SAT354

Enhancing the hepatitis B care cascade in Australia using a country-based testing program targeting new migrants: a cost-effectiveness model

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Background and Aims: If Australia is to successfully eliminate hepatitis B as a public health threat it will need to enhance the hepatitis B care cascade. Although the major population living with chronic hepatitis B (CHB) in Australia are born overseas from high endemic countries, there is no clear program or strategy to ensure this group are offered hepatitis B virus (HBV) testing or treatment. We postulate that incorporating an HBV testing program based on migrants' country of origin within the existing immigration medical exam (IME) currently undertaken by all permanent visa applicants to Australia is likely to increase the HBV care cascade. This study used a Markov model to assess the impact, costs and cost-effectiveness of a country-based pre-immigration hepatitis B testing program in Australia.
Method: The model calculated the difference in care cascade projection, disability-adjusted life-years (DALYs), difference in costs

and incremental cost-effectiveness ratio (ICER) among all people living with CHB in Australia in 2016–2030 in two scenarios: 1) status-quo: continued hepatitis B testing criteria for people taking the IME; and 2) a country-based testing program: migrants from countries with > = 2% hepatitis B prevalence were tested for HBV when taking the IME. Main model inputs included published demographics data of visa applications in 2014–2017 in Australia, country-specific CHB prevalence, Australia's care cascade progression data and CHB progression parameters. Healthcare funder's perspective was taken and costs were calculated based on all HBV testing costs paid by Australian Government.

Results: Under status-quo, an estimated 12% of new migrants with CHB were tested for HBV at the IME each year; the projected HBV care cascade among all people living with CHB in Australia in 2030 was 74% diagnosed, 35% in care and 20% on treatment. A country-based testing program was expected to diagnose around 83% of new migrants with CHB when they entering Australia; this scenario had a significant impact on the HBV care cascade in Australia, which was estimated to be 86% diagnosed, 47% in care and 26% on treatment among all people living with CHB in Australia in 2030. Compared to status quo, the scenario with a country-based testing program had an additional cost of A$0.3 billion if the HBV testing were at Australian Government's costs and averted 14,239 DALYs, giving an ICER of A $21,001 per DALY averted between 2016 to 2030. Sensitivity analysis showed that cost-effectiveness was influenced by disease progression rates and hepatitis B treatment costs.

Conclusion: A pre-immigration hepatitis B testing program based on migrants' country of origin would facilitate Australia to achieve 2030 hepatitis B elimination targets. Our model showed that such a program is likely to be highly cost-effective.

SAT355

Cost-effectiveness of mass screening for HCV in an Irish prison

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Background and Aims: A high proportion of PWID have ever been incarcerated in Ireland (70%) and a high proportion of prisoners have a history of injecting drug use (26%). Because of this, there is a high prevalence of HCV in prison populations (16%) in Ireland, which makes prison a high priority setting for undertaking HCV testing and treatment. We evaluate the cost-effectiveness of a mass HCV screening intervention in Mountjoy Prison in Dublin that screened 419 individuals, diagnosed 50 chronic HCV infections, and initiated 32 individuals on treatment. This is compared to the standard of care of intermittent screening on committal and in the community.

Method: An ingredients-based costing was used to cost of the screening and treatment in prison. Top down costings estimated the set-up and overhead costs. Standard of care costs were estimated through interview. A dynamic model of HCV transmission and disease progression among incarcerated and community PWID and ex-PWID was parameterised and calibrated using incarceration, demographic, HCV epidemiological and cascade of care data for Dublin or Ireland. The model used data directly from the intervention to project the resulting health benefits in terms of quality adjusted life years (QALYs) of the 1-year screening and linkage to care intervention over 50 years. The incremental cost effectiveness ratio (ICER) was calculated as the difference in costs divided by the difference in QALYs between the mass screening intervention and the standard of care comparator. Probabilistic sensitivity analysis (PSA) was used to determine the probability that the intervention was cost-effective compared to a willingness to pay threshold of €30,000 per QALY.

Results: The total direct costs of the intervention (not including treatment costs) was €81,415, with most costs being due to staff (43%). Over 50 years, the overall incremental cost of the intervention was €15,334 and the intervention gained 13 QALYs, giving a mean ICER of €1,200. All runs in the PSA were under the willingness to pay threshold.

Conclusion: Our analysis suggests prison mass screening could be a cost-effective initiative for increasing testing and linkage to care in prison in Ireland.

Viral Hepatitis A, B, C, D, E: Virology

SAT356

Hormone replacement therapy is associated with reduced liver cirrhosis risk and improved survival in treatment-naive hepatitis B- and/or C- infected postmenopausal women: a nationwide long-term population-based cohort study

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Background and Aims: Post-*menopausal hepatitis B virus (HBV) or hepatitis C virus (HCV) infected women* are likely to speed a *liver*

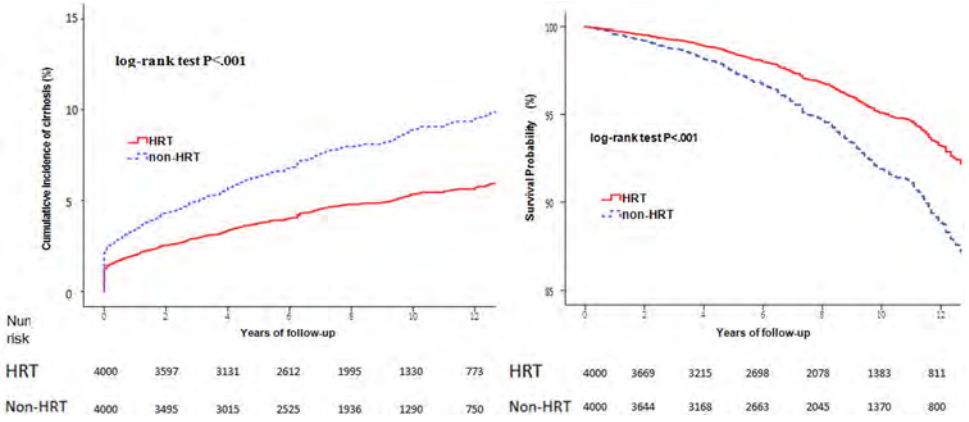

Figure: (abstract: SAT356)

fibrosis process, which will eventually advance to liver cirrhosis. It has not been fully investigated whether hormone replacement therapy (HRT) is beneficial to HBV and/or HCV infected women when they reach menopause age. The aim of this study was to evaluate the *severity of HBV and/or HCV* related *liver disease* in women in relation to the menopause and HRT.

Method: We enrolled 81,593 patients with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection between January 2000 and December 2013 from Taiwan's National Health Insurance Research Database (NHIRD). All diagnoses were coded according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). After excluding pre-existing other liver diseases, liver cirrhosis, or liver malignancies, the remaining 25,427 untreated HBV and/or HCV infection patients were grouped into patients (n = 11112) who were identified to have undergone HRT for at least 3 months and postmenopausal patients (n = 14315) who had not received HRT. After propensity score matching, 4000 patients with HRT were matched one to one to participants without HRT. The impact of HRT on liver cirrhosis and its major complications (esophageal varix, ascites, hepatic encephalopathy, hepato-pulmonary hypertension, hepato-renal syndrome, spontaneous bacterial peritonitis, coagulation disorders) were evaluated using multivariate analyses considering all putative confounding factors.

Results: In postmenopausal women, the estimated incidence rate of liver cirrhosis was lower in women who had received HRT, compared with a non-HRT cohort ($p < 0.001$) (left panel of the figure). Among cirrhotic patients, the estimated incidence rates of cirrhosis related esophageal varix, ascites, and hepatic encephalopathy were lower in women who had received HRT, compared with a non-HRT cohort ($p < 0.001$). The chance of survival was significantly higher in the HRT cohort than in the non-HRT cohort ($p < 0.001$) (right panel of the figure).

Conclusion: Our study reported that *HRT* significantly reduced the *risk* of *liver*-related complications. Menopause is associated with an increased liver cirrhosis risk in HBV- and/or HCV-infected women and it is preventable by HRT.

SAT357

Hepatitis B virus core protein variants observed in a first-in-human placebo-controlled study of a core protein inhibitor

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Background and Aims: Functional cure rates for chronic hepatitis B (CHB) virus infection are low, necessitating the development of new therapeutic strategies such as core protein inhibitors (CIs). AB-506 is a class II CI that binds hepatitis B virus (HBV) core protein, accelerating and misdirecting capsid assembly resulting in formation of empty viral particles. One of 20 subjects on active drug in the AB-506-001 first-in-human study did not show a serum HBV DNA response, which was subsequently found to correlate with a pre-existing core I105T variant. Here we describe additional HBV core variants observed in recruited subjects focusing on amino acid positions that may be of relevance to other molecules which access the same binding pocket.

Method: HBV DNA extraction was performed on plasma collected from the 24 non-cirrhotic, HBeAg-positive or -negative, HBV DNA-positive subjects enrolled in AB-506-001 (randomized 10:2 per cohort to AB-506 versus placebo) and 28 subjects that were screened but not enrolled in the study. Extracted DNA samples were subjected to HBV-specific PCR amplification followed by Illumina MiSeq next generation sequencing.

Results: Sequence analysis of viral genomes in the blood of CHB subjects at baseline revealed the pre-existing presence of multiple CI-relevant HBV core variants > HBVdb reported prevalence and in some cases co-existing in the same subject. In cell culture, T33N, T33S, I105T and T109S as single point mutations resulted in 2.5- to 356-fold change in EC_{50} of AB-506. In addition to the previously reported I105T non-responder (NR), the 1 active subject with T109S had the weakest response (−1.3 log_{10} HBV DNA) other than the NR. Subjects with T33N and T33S were not treated.

Table: Frequency of pre-existing HBV core variants in CHB subjects recruited to AB-506-001

	Screened Subjects (n=52)			Prevalence		
Variant	Placebo (n)	Active (n)	Not Randomized (n)	Observed (%)	HBVdb (%)[a]	AB-506 FC[b]
T33N	-	-	1	1.9	0.02	356
T33S	-	-	1	1.9	0.04	2.5
Y38F	1	3	9	25	3.1	1.6
Y38H	-	1	1	3.8	1.2	0.5
I105T	-	1	3	7.7	0.6	19
I105V	-	2	5	13	1.1	1.3
T109S	-	1	1	3.8	0.1	2.7
T109M	-	1	2	5.8	0.7	1.9
Y118F	-	-	1	1.9	0.4	not tested

[a]Within 10,975 HBV genome sequences archived as of Sep 12, 2019 at https://hbvdb.ibcp.fr.
[b]Fold-change (FC) of *in vitro* AB-506 EC_{50} values against point mutation in a genotype D background.

Conclusion: These findings highlight the importance of conducting molecular epidemiology studies to assess the prevalence of circulating CI-resistant variants as well as developing next-generation CIs with improved coverage of these variants.

SAT358

Clinical and molecular characterization of the human kidney as extrahepatic site of hepatitis E virus infection

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Background and Aims: During infection with the hepatitis E virus (HEV), viral RNA can be detected in a variety of patient's body-fluids including the urine. Recently, the excretion of infectious virions via the urine has been demonstrated. However, until know it is unclear whether detection of the virus in the urine reflects an extrahepatic replication site in kidney cells of the host.
Extrahepatic HEV replication might serve as a reservoir causing viral relapse after treatment and has implications for viral transmission.

In this study we characterized virus particles in the urine of long-lasting chronically infected patients and evaluated kidney-derived cells in vitro for their ability to support viral propagation.
Method: We utilized body-fluids (plasma, stool, urine) of patients within the SofE-trial (Clinical Trial Number: NCT03282474) which includes patients with long-lasting HEV infection. RNA-positive samples were analysed by density gradient and deep-sequencing methods of viral ORFs 1 and 2. Five different kidney-derived cell-lines (cancer and non-cancer) were evaluated for their ability to support viral propagation of Kernowp6 (HEV GT3) and for response to antiviral treatment. Furthermore, infection of primary porcine kidney cells and testing of kidney biopsies from HEV infected patients for HEV-RNA via FISH analysis to proof extrahepatic replication are ongoing.
Results: Out of 9 patients within the SofE-trial, all had detectable RNA in stool and plasma. In the urine (uRNA) 4/9 patients were HEV-RNA positive at screening and 2/9 at baseline (both uRNA positive at screening). uRNA abundance did neither correlate with viral titers in plasma nor kidney function. Gradient analysis revealed a quasi-enveloped status of the virus in the urine.
Deep-sequencing analysis of viral ORF1 and ORF2 identified point mutations specifically occuring in uRNA.
Two kidney cell-lines efficiently supported viral infection and replication to similar levels as the hepatoma cell-line HepG2. Of note, they displayed lower susceptibility to ribavirin treatment as compared to the control cell-line.
Conclusion: Our results point to a possible extrahepatic replication of HEV within the kidney. This has important implications for understanding viral extrahepatic tropism and may improve surveillance during treatment of chronically HEV-infected patients to avoid recurrence/relapses possibly caused by a remaining reservoir at extrahepatic sides such as the kidney.

SAT359

Establishment of human induced pluripotent stem cell-derived hepatocyte-like cells permissive for serum-originated hepatitis B virus infection and allowing for covalently closed circular DNA inhibitor drug screening

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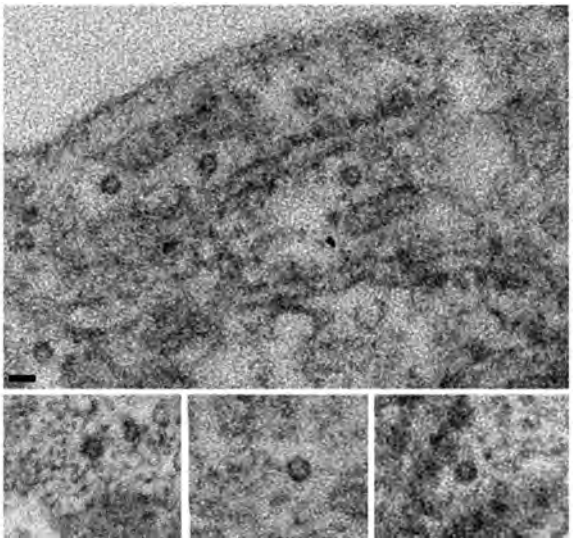
Background and Aims: Several lines of induced pluripotent stem cell-derived hepatocyte-like cells (iPS-HLCs) were established, permissive for hepatitis B virus (HBV) infection. However, such systems are limited by infection with a single, recombinant viral source, not suitable for studying infectivity of HBV containing sequence variations. Here, we established a line of iPS-HLCs permissive for serum-derived HBV infection.
Method: Human iPSC were differentiated into iPS-HLCs through a modified protocol. Permissiveness of iPS-HLCs for serum-derived HBV infection was verified. Serum samples from 119 chronic hepatitis B patients of various clinical conditions were used for infection. Virological factors including genotypes, HBV-DNA concentrations, qHBsAg levels, BCP mutations, precore mutations, and pre-S deletions were assayed for correlation with infectivity. Comparative cDNA microarray analysis was performed. Antiviral drug screening was conducted through assessing cccDNA levels under treatments of a panel of FDA-approved drugs.
Results: The differentiated iPS-HLCs contained a high level of sodium taurocholate cotransporting polypeptide, 9 folds higher than that in primary hepatocytes. Infection of serum-derived HBV was performed under a multiplicity of infection (MOI) of 10. The success of infection was confirmed by detection of HBV-RNA, viral proteins, viral particles under electron microscopy, and cccDNA. Post-infection cellular HBV-DNA levels could be suppressed by entecavir and tenofovir treatments. Comparative gene expression profiling showed activation of several cancer-related pathways after HBV infection. Under the same MOI, 119 samples were used for iPS-HLCs infection assays. Univariate followed by multivariate linear regression analysis revealed that the BCP G1719T mutation ($P = 0.002$) and qHBsAg level ($P = 0.016$) were independent predictors for infectivity. The iPS-HLCs were permissiveness for serum-derived vaccine escape HBV mutants. Finally, a panel of FDA-approved drugs ($n > 1400$) was used for cccDNA inhibitor drug screening. Suppression of cccDNA was observed in several candidate drugs, which were known inhibitors of signaling pathways capable of enhancing HBV replication.



Conclusion: A line of iPS-HLCs permissive for serum-derived HBV infection were established. This system was suitable for studying infectivity of HBV carrying naturally occurring or pathological mutations. It also served as a useful tool for anti-HBV drug discovery.

SAT360

Farnesoid X receptor alpha ligands inhibit hepatitis delta virus replication in vitro independently of their effect on hepatitis B virus

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Background and Aims: Hepatitis delta virus (HDV) is a satellite of hepatitis B virus (HBV), both using the Sodium Taurocholate Co-Transporting Polypeptide (NTCP), the main transporter of bile acids (BA) in the liver, to enter hepatocytes. Links between BA and HBV infection are not limited to the entry step as we previously showed that the farnesoid X receptor alpha (FXR), the nuclear receptor of BA, was a proviral factor for HBV and that FXR ligands acted as inhibitors of HBV replication. Regarding HDV, excepting the role of NTCP in viral entry, putative links between BA metabolism and HDV replication have not been yet explored. We thus wanted to determine whether FXR also played a role in HDV life cycle.
Method: In vitro HDV mono-infections or HDV/HBV co-infections and super-infections were performed in differentiated HepaRG (dHepaRG) cells and primary human hepatocytes (PHH). Cells were

treated with several FXR ligands: 6 -ECDCA, a BA analog and two synthetic ligands, GW4064 and tropifexor. The impact on distinct forms of HDV RNAs was analysed by quantitative PCR, Northern Blot and Run-On experiments. Analysis of HDV proteins was performed by immunofluorescence (IF) and Western Blot (WB), using antibodies against HDV antigens.

Results: In HDV/HBV co- or super-infection models, a 10 -day treatment with 10 μM of GW4064 decreased total intracellular HDV RNA in dHepaRG cells and PHH by 60% and 40%, respectively. Northern blot and Run-On experiments showed that both HDV genomic RNA and nascent viral RNA were affected by such treatment. IF staining and WB of infected cells showed that FXR ligands also decreased the amount of intracellular viral proteins. Both forms of delta antigens, small and large, were equally decreased, by around 75%, as revealed by WB analysis. Importantly, this inhibitory effect of FXR ligands on HDV replication was also observed in HDV mono-infected dHepaRG cells. Finally, three distinct FXR ligands, i.e. GW4064, 6 -ECDCA and tropifexor, showed comparable efficacy, indicating the specificity of action.

Conclusion: FXR ligands inhibit in vitro HDV replication. This inhibitory effect is independent of their previously identified antiviral properties against HBV. Mechanisms underlying this inhibitory effect are under investigation. As current therapeutic strategies are limited for HDV-infected patients, FXR may represent a new and attractive target for HDV antiviral therapy.

SAT361

Analysis of hepatitis B virus quasispecies in circulating viral DNA and RNA: are genotype and complexity different?

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Background and Aims: The study of Hepatitis B virus (HBV)-RNA containing virion-like particles allows monitoring intrahepatic HBV-RNA levels and is potentially useful for viral quasispecies (QS) analysis in patients with suppressed circulating HBV-DNA. Up to date, the HBV-RNA QS has not been studied in untreated chronic hepatitis B (CHB) patients with detectable levels of circulating HBV-DNA. The aim of the present study was to compare circulating HBV-DNA and RNA QS in a group of untreated CHB patients.

Method: A serum sample from 10 untreated CHB patients was selected: 6 (60%) HBeAg positive (+), median levels of HBV-DNA 1.25×10^8 IU/mL (IQR 1×10^8–3.9×10^8 IU/mL) and ALT 134 IU/L (IQR 74.3–159.3 IU/L). HBV-DNA and HBV-RNA were isolated from each serum sample. Isolated HBV-RNA was treated with DNAse I and retro-transcribed into cDNA. To ensure that no HBV-DNA was present, a qPCR was performed after DNase I treatment. HBV genotype and QS complexity were determined by next-generation sequencing (NGS, Miseq, Illumina) in the 5′ region of the HBV X gene (HBX, nt 1255-1611). HBV QS complexity was analyzed by the Rare Haplotype Load (RHL), a non-biased diversity index that measures enrichment of QS in very low frequency minority genomes, with little sensitivity to the differences in sequence coverage (PLoS ONE 2018;13:1–17).

Results: A total of 1.90×10^6 sequence reads were obtained, 1.22×10^6 for HBV-DNA and 6.77×10^5 for HBV-RNA. The HBV genotype mixtures were similar in DNA and RNA in all patients, main genotypes were 2 A, 1 C, 2 D, 2 E and 3 F. HBV QS complexity showed a heterogeneous behaviour between patients, but globally it was greater in DNA than in RNA ($p = 0.037$). Comparing the results according to the HBeAg, the DNA and RNA QS complexity was similar in HBeAg (+) patients (Figure A) while 3/4 HBeAg (–) patients showed a greater complexity in DNA (Figure B).

Conclusion: The HBV genotype mixture did not show significant differences between HBV-DNA and RNA QS, suggesting that circulating viral RNA could be an appropriate substrate to analyse QS during HBV-DNA suppression. Greater QS complexity in DNA than RNA suggests an increased presence of low frequency HBV genomes in DNA QS [more evident in HBeAg (–) than (+)], likely due to the error-prone reverse transcription origin of HBV-DNA. Funding: Instituto de Salud Carlos III (grant PI18/01436), co-financed by the European Regional Development Fund (ERDF).

SAT362

Mitochondrial DNA damage and mitochondrial dysfunction in patients with chronic hepatitis B

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Background and Aims: Mitochondria serve as a platform for the antiviral innate immune and inflammatory responses. Some hepatitis B virus (HBV) proteins are imported into the mitochondria, increase the mitochondrial oxidative stress and impair mitochondrial function which may account for fibrosis progression.

The aim of our study was to investigate the effects of HBV-induced mitochondrial oxidative stress on mitochondrial (i) DNA (mtDNA), (ii) function, (iii) dynamics and (iv) unfolded protein response (UPRmt) in Chronic Hepatitis B (CHB) patients with minimal to advanced fibrosis.

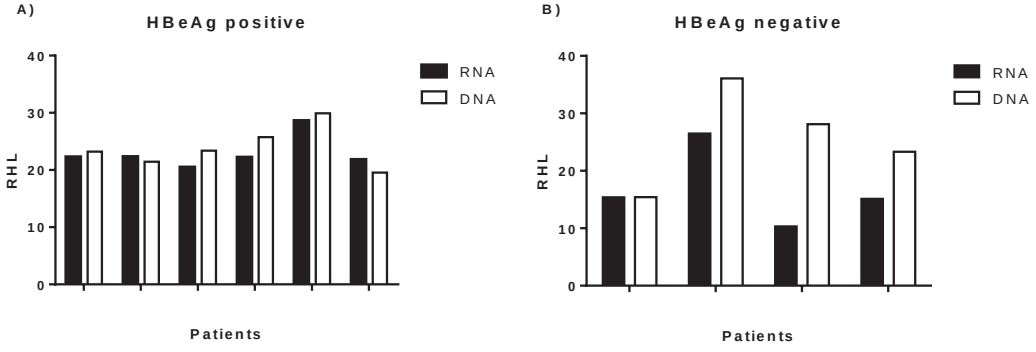

Figure: (abstract: SAT361): Analysis of rare haplotype load (RHL) in HBeAg positive (A) and negative patients (B).

Methods: Fifty naïve CHB patients (n = 50) with different fibrosis stages [Metavir Scores: F0 (n = 10), F1-2 (n = 25) and F3-4 (n = 15)] were evaluated for mtDNA damage, mitochondrial function and dynamics. Total DNA, RNAs and proteins were purified from liver samples of these patients. Liver ATP was determined by chemiluminescence and mtDNA damages were investigated by Southern blot and PCR. The expression of the following genes was assessed (RT-qPCR and Western-Blotting): subunits 1 (CO1), 2 (CO2) and 4i1 (COX4i1) of the complex IV of the respiratory chain, PGC1α and mTFA (transcriptional factors for mitochondrial biogenesis), LonP1 peptidases, HSP60 and HSP70 chaperones (mitochondrial unfolded protein response, UPR^{mt}).
Results: Massive mtDNA damage associated with a significant drop of Hepatic ATP levels were observed in livers from CHB patients. Compared to CHB patients with moderate fibrosis (F1-2), we observed in CHB patients with an advanced fibrosis (F3-4) alterations in the mRNA expression of the complex IV of the mitochondrial respiratory chain with a significant decrease of CO1 (1,09 ± 0,57 *vs* 0,49 ± 0,26; $p < 0.001$) and CO2 (1,34 ± 1,0 *vs* 0,99 ± 0,62; $p < 0.05$), alterations of the mitochondrial biogenesis process with a significant decrease of PGC1α (0,8 ± 0,6 *vs* 0,5 ± 0,3; $p < 0.05$) and mTFA (1,2 ± 0,9 *vs* 0,6 ± 0,4; $p < 0.05$) transcription factors and alterations of UPRmt process with a significant decrease of HSP60 (1,1 ± 0,6 *vs* 0,7 ± 0,3; $p < 0.05$), HSP70 (0,8 ± 0,4 *vs* 0,5 ± 0,2; $p < 0.05$) chaperones and LonP1 peptidase (1,3 ± 0,6 vs 0,8 ± 0,2; $p < 0.01$). COX4i1 mRNA expression remained unchanged whatever fibrosis stage. Protein expression of CO1, CO2, PGC1α and mTFA was significantly decreased (at least 50%) and correlated with the severity of fibrosis.
Conclusion: Massive mtDNA damage associated with alterations of the mitochondrial function, biogenesis and unfolded protein responses were observed in CHB patients. The extent of these mitochondrial lesions is associated with advanced HBV-mediated fibrosis. HBV increased mitochondrial oxidative stress which is known to degrade mtDNA. Combined together, such mitochondrial alterations concomitantly contribute to a major mitochondrial dysfunction that may play an important role in the pathophysiology of CHB and the development of fibrosis in these patients.

SAT363
Differential HBV RNA and quantitative HBsAg kinetics between HBeAg(+) and HBeAg(−) patients with chronic hepatitis B on nucleos(t)ide analogues (NA)

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Background and Aims: Functional cure with HBsAg clearance is a desirable treatment goal. Patients with HBeAg (−) chronic hepatitis B (CHB) have lower baseline quantitative HBsAg (qHBsAg) levels but do not have higher rate of HBsAg loss on NA therapy. We aim to examine the on-treatment HBV RNA and qHBsAg kinetics between HBeAg (+) and (−) patients.
Method: CHB patients on NA for at least 1 year with available stored serial sera from baseline were included in this analysis. Serum HBV RNA was measured using the Abbott research assay (Sensitivity: 1.65 log U/ml). Serum qHBsAg titers were determined by Abbott Architect assay (Sensitivity: 0.05 IU/ml).
Results: This predominantly Asian (95%) cohort consisted of 29 HBeAg(+) and 12 HBeAg(−) CHB patients. The duration of therapy was similar for the HBeAg (+) and (−) groups (58 vs. 55 months, p = 0.9). 14 subjects achieved HBeAg loss after 5 to 74 months of therapy. None of the HBeAg(−) subjects had functional cure. The HBeAg(−) patients had significantly lower baseline DNA, RNA and qHBsAg levels compared to the HBeAg(+) ones, and reached optimal HBV DNA suppression (<1.3 log IU/ml) fastest. The decline of RNA and qHBsAg from baseline to time of DNA <1.3 log IU/ml, in contrast, was much slower among the HBeAg(−) patients [Table]. The 14 patients who achieved HBeAg loss had the greatest initial reduction in RNA and qHBsAg levels associated with HBV DNA suppression. At last follow up, 5 of 14(35%) had RNA <1.65 U/ml but only 1 had HBsAg loss. In contrast, none of the patients who remained HBeAg(+), and only 5 (42%) HBeAg(−) patients, achieved RNA <1.65 U/ml. The annual log reduction of qHBsAg from baseline to last follow up was significantly slower among the HBeAg(−) patients. [Table].
Conclusion: In this cohort, HBV RNA kinetics differentiated HBeAg (+) CHB patients with and without HBeAg loss on long-term NA therapy. HBeAg(−) subjects achieved optimal HBV DNA suppression the fastest but had the slowest decline in HBV RNA and qHBsAg levels over time. The kinetics of HBV RNA and qHBsAg decline elucidated the low rate of treatment-related HBsAg loss among the HBeAg(−) patients.

Table: (abstract: SAT363)

Mean	NA-induced HBeAg loss (N = 14)	No NA-induced HBeAg loss (N = 15)	HBeAg(−) (N = 12)	Anova P value
Baseline HBV DNA (log IU/ml)	7.3	7.4	4.9	0.0001
Baseline HBV RNA (log U/ml)	6.0	7.0	2.9	0.0001
Baseline qHBsAg (log IU/ml)	4.1	4.1	2.7	0.0001
Time to HBV DNA<1.3 log IU/ml (months)	27.8	33.8	7.6	0.03
% RNA decline from baseline to DNA<1.3	47%	25%	16%	0.01
% qHBsAg drop from baseline to DNA<1.3	26%	15%	6%	0.04
Annual reduction of qHBsAg from baseline to last follow up (log IU/ml/year)	0.36	0.23	0.09	0.01

SAT364
Role of hepatitis C virus core antigen in HIV-HCV co-infected and chronic kidney disease patients on hemodialysis: expanding the HCV horizon of diagnostics

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Background and Aims: The prevalence of Hepatitis C Virus (HCV) infection in chronic kidney disease patients (CKD) on hemodialysis (HD) patients and in patients with HIV-HCV co-infection is greater than in the general population. Screening for HCV infection in this population is associated with false negative HCV antibody results. HCV core antigen (cAg) can be an important diagnostic marker to screen for HCV infection in such patients. This study investigates the correlation of HCV c Ag with the current gold standard of HCV RNA test in both of these difficult to diagnose patient groups.
Method: Stored sera of 111 consecutive treatment-naive patients tested anti-HCV positive for whom HCV-RNA (Abbott RealTime PCR) was requested were analysed for HCVAg (Abbott ARCHITECT) in order to evaluate the correlation between the two parameters in both HIV-

HCV co-infected, n = 83 and HCV infected CKD patients on HD, n = 28. The differences between percentages were evaluated by Fisher's exact test, while mean and median values were compared by Student's t test, respectively. All differences were considered significant for a p value <0.05.

Results: Overall in 111 anti-HCV-positive sera, 101 were positive for both HCV Ag (≥3 fmol/L) and HCV RNA (>15 IU/mL), 6 were negative for both tests, while 4 were positive to HCV RNA only. The sensitivity and specificity for HCV Ag in predicting HCV RNA were 96.1% and 100%, respectively. This was similar in both the groups of patients. Out of 105 patients (94.5%) tested positive for HCV viremia, 65 (61.9%) were of genotype 3, 25 (23.8%) of genotype 1 and 15 of other genotypes. In HIV -HCV coinfected group a strong positive correlation was seen between HCV RNA and HCV-Ag ($r = 0.960$, $p < 0.001$). Similarly in CKD group on HD correlation between RNA and Ag was ($r = 0.83$, $p < 0.001$). No false positive Ag was detected in any of the group and RNA was positive in only 4 patients with Ag negative (3 in HIV-HCV coinfected and 1 in CKD on HD group). In all these 4 patients HCV RNA levels were <3 $\log_{10}$ IU/ml.

Conclusion: Given the strong positive correlation between HCV-Ag and HCV RNA in both these HCV infected patient population, we propose that HCV-Ag can be a more cost and time efficient alternative to the current two-step diagnostic process.

SAT365

Characterization of acute hepatitis C virus infection and transmission clusters by next-generation sequencing among people who inject drugs in Catalonia

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Background and Aims: Dried-blood spot (DBS) samples have proven useful to improve access to hepatitis Hepatitis C virus (HCV) testing among people who inject drugs (PWID). We previously showed that HCV isolates can also be genetically characterized from DBS samples by next-generation sequencing generating useful epidemiological information, such as the identification of acute infections and transmission clusters. In order to inform preventive public health interventions, we aimed to assess factors associated with acute HCV infection and belonging to a transmission cluster.

Method: Current PWID (N = 410) attending harm reduction services in Barcelona were recruited in 2016–17 (HepC*detect* II study). DBS samples were collected from all participants, and plasma from 300 cases. All samples were tested for HCV RNA, and a 389-bp region of the NS5B gene was amplified in viremic individuals. Sequence libraries were indexed and subjected to Illumina paired-end sequencing (2 × 250 cycles, MiSeq). The HCV intra-host genetic variability estimate Shannon entropy (SE) was used to identify acute infections. A set of well-defined acute (<6 months) and chronic infections were used to establish a SE cut-off by ROC curve analysis. Transmission clusters were also identified from sequencing data. An epidemiological questionnaire was administered and risk factors for acute infection and phylogenetic clustering were identified by multivariate logistic regression analysis.

Results: Based on ROC curve analysis, 13.5% (29/215) viremic individuals were identified as acute HCV infection (five mixed infections were excluded). Factors associated with acute infection included age <30 (AOR = 8.09), injecting less than daily (AOR = 4.35), ≤5 years of injected drug use (AOR = 3.43), sharing cocaine snorting straw (AOR = 2.89), and being unaware of their HCV status (AOR = 3.62). Additionally, 46.8% (103/220) of viremic cases were involved in transmission pairs/clusters; age ≤30 years (AOR = 6.16), acute infection (AOR = 5.73), and infection with subtype 1a (AOR = 4.78) were independently associated with this condition.

Conclusion: The molecular epidemiology techniques carried out, which can also be performed from minimally invasive DBS samples, have allowed us to characterize for the first time in our setting the profile of PWID with acute infection and those currently involved in HCV transmission. This information could help assess harm reduction programs and monitor incidence of HCV infection in this key collective.

SAT366

Mathematical modeling of early hepatitis D virus kinetics in transgenic-hNTCP mice

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Background and Aims: Understanding early hepatitis D virus (HDV) dynamics post infection is lacking. Here, we characterized the early kinetics of HDV post inoculation (pi) and used mathematical modeling to provide insights into HDV-host dynamics.

Method: Transgenic (tg) mice expressing human NTCP (hNTCP) (n = 20), the receptor for hepatitis B virus and HDV, and non-tg control animals (n = 30) were inoculated intravenously with 10^9 genome equivalents (GE) of cell-culture produced HDV (genotype 1). Serum HDV viremia was quantified by RTqPCR at 1 min and then every 2 hour (hr) in the serum over the first 96 hr post inoculation (pi). An additional 9 non-tg mice were inoculated with 10^9 GE at time 0 and again at 4 hr pi. A mathematical model was developed and calibrated to measured serum HDV kinetics.

Results: No significant difference ($p = 0.07$) was found in median HDV RNA 1 min pi between non-tg (8.5 $\log_{10}$ cps/ml) and tg-hNTCP mice (8.8 $\log_{10}$ cps/ml). A biphasic decline in HDV was observed in both non-tg and tg-hNTCP mice consisting of rapid decline first phase (slope = 1.4 $\log_{10}$/hr and 1.6 $\log_{10}$/hr, respectively) that was lasted 2 hr pi, followed by a slower decline second phase (slope = 0.14 $\log_{10}$/hr and 0.2 $\log_{10}$/hr, respectively) until 14 hr pi when HDV RNA became lower than the limit of detection (Fig. 1 left). Notably, there was no difference in HDV decline slopes between non-tg and tg-hNTCP mice suggesting negligible effect of HDV entry on viral decline and no evidence of viral production. As such, we developed a mathematical model assuming no production of new virions and that free HDV can be cleared (parameter c) or bound to a non-specific binding compartment (parameter k_{on}) and released into the circulation with off-rate constant, k_{off}. The model reproduces the biphasic decline (Fig. 1 left) and suggests that the first phase of HDV decline mainly reflects HDV clearance with estimated HDV half-life $t_{1/2} = 2.4$ min with 95% confidence interval, [1.2, 46.2] min in both non-tg and tg-hNTCP mice, respectively. The second phase of HDV decline mainly represents the binding compartment off-rate, which was 0.39 [0.02, 0.7]/hr for non-tg mice and 0.48 [0.02. 0.9]/hr for tg-hNTCP mice. To validate the model, we challenged the model with the HDV kinetics obtained from non-tg mice that were re-inoculated with HDV at 4 hr pi (Fig. 1 right). Interestingly, the model reproduces the data if a

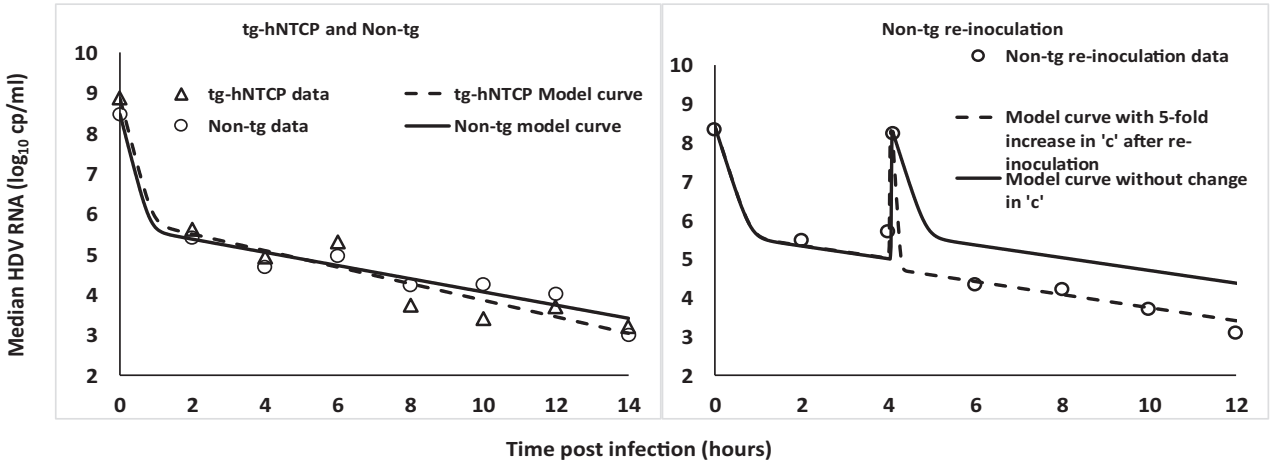

Figure: (abstract: SAT366)

5-fold increase in the HDV clearance rate is assumed after the re-inoculation at 4 hr pi (Fig. 1 right).
Conclusion: The unexpected biphasic early HDV kinetics observed in mice can be modeled by assuming the existence of a binding compartment with a constant off rate. The model predicts that HDV clearance is ~5-fold enhanced after re-inoculation of HDV after 4 hr pi. However, further experiments and theoretical efforts are needed to formalize these results and predictions.

SAT367
Prospective study of viral hepatitis in pregnancy and its vertical transmission in the northeast region of India
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Background and Aims: Acute viral hepatitis is the most common cause of jaundice in pregnancy and pregnant women are at increased risk of morbidity and mortality.
Methods: This is a prospective, ongoing multi centric study; Sera of 1046 pregnant women in any trimester, attending the antenatal clinics of 4 selected hospitals were analyzed for markers of hepatitis A, B, C and E viruses. Cord blood from the positive mothers is being collected and evaluated for vertical transmission, if any.
Results: Of the pregnant women tested, 1.9% (20/1046) were found positive for HBsAg, 0.6% (6/1044) for anti HCV, 0.5% (4/734) for IgM anti HEV, 5.8% (32/548) for IgG anti HEV, 0.1% (1/782) for IgM anti HAV, and 19.8% (93/469) for IgG anti HAV. While, 16 HBsAg positive pregnant women have delivered and 56.2% (9/16) of cord blood was found to be positive, on the other hand, none of the cord blood was found positive in the 3 HCV positive pregnant women delivered.
Conclusion: Prevalence of HBsAg and anti HCV in pregnant women was found to be 1.9% and 0.6% respectively. The rate of vertical transmission is reported to be 56.2% among HBsAg positive pregnant women tested, which was however not observed in anti HCV positive mothers. Further, the prevalence of acute hepatitis E was 0.5% and the marker for previous infections was 5.8%, whereas acute hepatitis A was prevalent in mothers with 0.1% and the marker for previous infection to be 19.8%.

SAT368
Usefulness of dried plasma spots using a plasma separation card for serological diagnosis of chronic hepatitis B and C and reflex viral load testing
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Background and Aims: Increasing diagnosis rate of hepatitis B and C is one WHO objective to achieve viral hepatitis elimination in 2030. However, access to diagnosis in certain regions with suboptimal infrastructure or in special populations is limited by the lack of accessibility to blood extraction methods and low accuracy of rapid diagnosis tests. In these circumstances, the WHO guidelines recommends the use of alternative sample types. The cobas® Plasma Separation Card (PSC) in a new device that generates dried plasma spots however there is no data on its usefulness for HCV and HBV serology screening (HBsAg and/or anti-HCV). Our goal was to correlate the results of HBsAg, anti-HBc, anti-HCV, HBV-DNA and

HCV-RNA in PSC vs plasma in chronic hepatitis B (CHB) and/or C (CHC) patients and its usefulness in reflex molecular testing.
Method: Observational study of consecutive samples of CHB and/or CHC patients. HBV and HCV serology and viral loads were tested on plasma samples obtained by venepuncture and on the PSC (Roche Diagnostics) prepared from finger puncture. HBsAg, anti-HBc and anti-HCV were determined in the cobas® 8000 System (Roche Diagnostics). In HBsAg positive or anti-HCV positive cases, HBV-DNA or HCV-RNA were respectively quantified as reflex test using a second spot in the same PSC in the cobas® 6800 System-(Roche Diagnostics).
Results: 98 patients were included: 56 HBsAg positive, 40 anti-HCV positive, 2 HBsAg+, anti-HCV positives. A 100% correlation was observed in serological markers between PSC card and the conventional method. HCV RNA in PSC and in conventional plasma samples was detectable in 16 (38%) of 42 anti-HCV positive with a R^2 of 0.91 (HCV-RNA 5.6 ± 1.7 logUI/mL vs 3.9 ± 1.4 PSC). HBV DNA in PSC was detected in 29 (50%) of 58 HBsAg positive samples with an R^2 of 0.95 to plasma (3.5 ± 1.9 logUI/mL vs. 1.5 ± 2 PSC). In plasma samples with HBV-DNA>3 logUI/mL 93% was detectable by PSC while in those with HBV DNA ≤3 logUI/mL PSC was only detectable in 20% of samples.
Conclusion: The performance of dried plasma samples in PSC for detection of serological markers of hepatitis B and C virus infection is excellent and comparable with conventional techniques. Viremia studies on PSC cards correlates very well with conventional systems allowing viral load reflex testing, but detecting 2 log less of HBV-DNA. However, this does not impact on the selection of patients candidates to therapy since this is recommended when HBV-DNA levels are >3 logUI/mL.

SAT369
Validity of a point-of-care viral load kit for hepatitis B in a low-income setting
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Background and Aims: A major obstacle to scale up treatment of chronic hepatitis B (CHB) in low-income countries is the lack of access to hepatitis B virus (HBV) viral load testing. The recent launch of the first point-of-care HBV viral load kit from GeneXpert could overcome this problem. Such new technology needs, however, real-life testing before it can be implemented into routine use. The current study aimed to validate the new GeneXpert viral load kit against the gold standard from Abbott.
Method: In 2015, we established a cohort of patients with CHB in Ethiopia. We randomly sampled 123 patients from this cohort and assessed viral load with both the new GeneXpert kit and the Abbott RealTime HBV assay (gold standard) at the same time in each patient. We assessed the validity of GeneXpert by calculating the correlation between the two tests and performing a Bland-Altman plot. We assessed the diagnostic performance of GeneXpert (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)) in identifying CHB patients with a viral load ≥2000 IU/mL in the Abbott assay. We used the Youden index of the receiver operator characteristics (ROC) curve to suggest an optimal cut-off for GeneXpert to identify CHB patients with a viral load ≥2000 IU/mL in the Abbott assay.
Results: We found a high correlation between the viral load assessed by GeneXpert and Abbott (r = 0.943, p < 0.001, Figure). The Bland-Altman plot showed no bias between the two tests and an on average 0.24 log10 IU/mL higher viral load result with the GeneXpert compared to Abbott. Using the European cut-off of 2000 IU/mL in both tests, the GeneXpert had a sensitivity of 94%, specificity of 69%, PPV of 68%, and NPV of 94% to identify the same individuals above the threshold in the Abbott assay. The optimal GeneXpert cut-off suggested by the ROC curve is 4190 IU/mL. With this cut-off, sensitivity and specificity are both 90%, PPV = 86% and NPV = 93% (area under the ROC curve = 0.95).

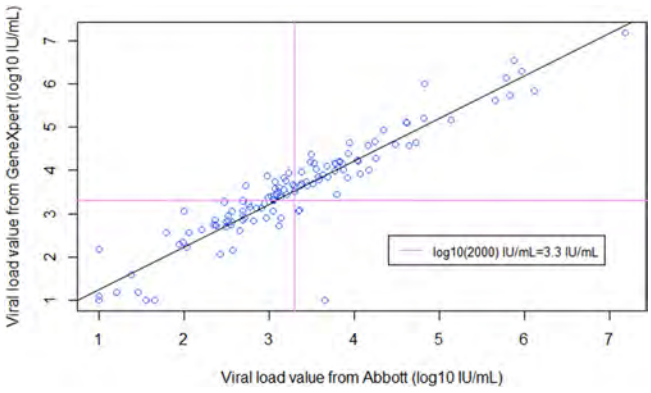

Figure: Correlation of viral load measurement from GeneXpert and Abbott on the logarithmic scale (n = 123). The pink lines represent a cut-off of 2000 IU/mL.

Conclusion: We found good validity of the new GeneXpert kit in a real-life setting with a high correlation with the Abbott assay and good sensitivity and specificity. This new point-of-care viral load kit can enable access to treatment for CHB patients in low-income countries.

SAT371
Mechanism of action studies of inarigivir, a novel immunomodulator against chronic hepatitis B
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Background and Aims: In the Phase IIa Achieve® clinical trials, Inarigivir caused significant reductions of HBV DNA, HBV RNA, HBsAg and HBcrAg. Inarigivir, an oral dinucleotide prodrug, metabolizes to the active SB 9000 *in vivo*. As a pan antiviral agent, it activates human Retinoic Acid-Inducible Gene (hRIG-I), for the induction of innate and adaptive immunity. Summarized here are the mechanism of action (MOA) studies.
Method: Demonstration of direct binding to hRIG-I by SB 9000. a) Dissociation constant Kd of hRIG-I binding was ascertained by surface plasmon resonance using streptavidin chips coated with biotin-conjugated SB 9000 (BSB). b) BSB was incubated with anti-DDK antibody bound to FLAG-tagged hRIG-I and ELISA performed using Avidin/HRP-conjugate. c) Fluorescent enhancement assays were performed to assess Inarigivir/SB 9000-mediated translocation of hRIG-I on dsRNA. d) BSB was incubated with A549 cell lysates expressing FLAG-tagged hRIG-I, the bound proteins visualized by Western blot using anti-FLAG antibody. e) Binding of SB 9000 to the *Helicase* domain of hRIG-I was assessed by immuno-precipitation using hRIG-I mutants in A549 cells. f) Cellular co-localization of SB 9000 with hRIG-I in A549 cells was assessed using confocal microscopy. Demonstration of hRIG-I-dependent induction of pIRF3 and IFNs. a) SB 9000 was incubated ± ATP with a reconstitution complex of hRIG-I, IRF3, ubiquitin, ubiquitin *ligases*, mitochondrial/cytosolic fractions, and phosphorylated IRF3 detected by Western blot. b) HepG2/A549 cells were treated with Inarigivir and IFN-beta

assessed by ELISA; hRIG-I specificity was ascertained using siRNA silencing of hRIG-I. c) WHV-infected woodchucks (n = 5/group) were treated once daily orally with Inarigivir for 12 weeks at 15 or 30 mg/kg and IFNs, IL-6, CXCL10, OAS1 and ISG15 mRNA in blood and liver measured by qPCR and hepatic RIG-I assayed by immunohistochemistry.

Results: SB 9000 directly bound to hRIG-I *via* its *Helicase* domain with Kd of 12 picomolar and co-localized with hRIG-I in cells. SB 9000 activated hRIG-I to induce ATP-dependent phosphorylation of IRF3. SB 9000 induced hRIG-I-dependent IFN production in cells. The antiviral activity of Inarigivir in woodchucks was associated with dose-dependent induction of IFNs, ISGs and RIG-I.

Conclusion: The *in vitro* and *in vivo* studies support the MOA of Inarigivir involving the activation of hRIG-I to produce IFNs and cytokines and mediate antiviral activity in CHB patients.

SAT372

A systematic assessment of acute viral hepatitis and chronic liver diseases in northeast India with special reference to strengthening of laboratories in the region

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Background and Aims: In India, viral hepatitis caused by hepatitis viruses A through E remains to be a major public health problem. HAV and HEV are important causes of acute viral hepatitis and acute liver failure (ALF). On the other hand, infection with HBV, HCV or HDV, which may present as acute hepatitis some time have the potential to cause persistent infection and may progress to liver cirrhosis or liver cancer to become life-threatening.

Methods: In this cross-sectional ongoing multicentric study, serological prevalence analysis of viral hepatitis A, B, C, and E was performed in 536 randomly selected subjects across selected tertiary care and district hospitals of 8 northeastern states of India. Cases were divided into acute hepatitis, acute liver failure, chronic hepatitis, cirrhosis and hepatocelluar carcinoma and were tested for serological markers.

Results: The overall prevalence of hepatitis B virus surface antigen (HBsAg), anti hepatitis B virus surface protein antibody (HBsAb), anti hepatitis B virus core protein anti body (HBcAb), hepatitis B envelope antigen (HBeAg) and anti hepatitis B envelope antibodies (HBeAb) was 30.4% (163/536), 18.6% (87/468), 35.8% (168/469), 6.8% (27/398) and 18.7% (75/402) respectively. The prevalence of hepatitis D antibody was 1.8% (3/163). The prevalence of hepatitis C virus antibody (anti-HCV) was 11.3% (60/531). The prevalence of acute hepatitis A anti HAV IgM and hepatitis E anti HEV IgM was 9.1% (22/240) and 5.6% (21/374) respectively. Meanwhile, the serological markers for previous infection of hepatitis A anti HAV IgG and hepatitis E anti HEV IgG was 36.9% (150/407) and 9.8% (40/407) respectively.

Conclusion: The data so far shows the epidemiological transition of hepatitis A leading to an increased incidence of symptomatic HAV infection in adults. Further, the pattern of HEV infection was observed different among the different ethnic groups and regions of the country.

SAT373

From in vivo to in vitro: ex vivo studies using primary human hepatocytes from chronically diseased liver-humanized FRG® KO mice

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Background and Aims: Liver-humanized FRG KO mice are useful for in vivo studies in many application areas including infectious diseases, NAFLD/NASH, gene editing/therapy, metabolism, and pharmacology/toxicology.

Cryopreserved primary human hepatocytes can be thawed and plated, but have a limited life-span in vitro. Fresh primary human hepatocytes, either isolated from biopsies or from liver-humanized mice, have a longer life-span in vitro of at least 30 days.

The life-span of in vitro cultures of primary hepatocytes is too short to study chronic liver diseases like hepatitis B or non-alcoholic fatty liver disease. It takes up to 14 days to induce a chronic infection state with HBV, after which only a small window remains to test novel therapeutics. For the study of NAFLD or NASH, there is currently no standardized in vitro model available.

Method: Chronic liver diseases were induced in liver-humanized FRG KO mice. Animals were either infected with HBV, or received a high-fat diet to induce NAFLD/NASH. Eight to twelve weeks after the start of the experiment, animals were sacrificed and after perfusion, human hepatocytes were purified and plated for in vitro studies.

Results: Primary human hepatocytes isolated from liver-humanized FRG KO mice infected with HBV were up to 100% positive for HBcAg. Without the need to infect the hepatocytes in vitro, the efficacy of novel therapeutics can be tested the day after plating and during multiple days, followed by a wash-out period during which a rebound can be measured. No negative effects on cell health or plating efficacies were observed when comparing naïve vs infected primary hepatocytes isolated from liver-humanized mice.

The isolation of hepatocytes from liver-humanized FRG KO repopulated with human PNPLA3-148M hepatocytes and fed HFD is not hampered by the steatotic state of the cells. After plating, the cells survived comparable to hepatocytes from control humanized animals. The culture media was supplemented with lipogenic factors to maintain the diseased state of hepatocytes isolated from mice that received a high-fat diet. In comparison, when using standard hepatocyte culture media, lipid droplets gradually decreased over the course of 5 days. This can be explained by the lack of lipogenic triggers.

Conclusion: Liver-humanized mice are proven to be useful for long-term in vivo studies for several applications. For high-throughput in vitro studies, they can be a valuable source of chronically diseased hepatocytes. Compared to patient-derived hepatocytes, the liver-humanized mice can provide a readily available source of hepatocytes of known origin, with a specific disease induced, and for which control animals can provide hepatocytes from the same donor but without the disease of interest.

SAT374

The head-start project Georgia: a three-armed, cluster, non-randomised trial of the effectiveness of two novel models of HCV confirmatory testing in harm reduction sites (HRS) in Georgia

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Background and Aims: Georgia, a middle income country with an estimated population of 3.7 million people, is among the world's highest-burden countries, with an HCV prevalence of 6.7% in the general population and a higher burden of disease in high risk populations especially PWID. In 2015, Georgia embarked on an elimination programme, however significant gaps remain in case finding and linkage to care. In particular, although screening programs have largely been decentralised for high risk groups, viremic testing remains a bottleneck for PWID accessing care. Here we describe two novel models of viremic testing that aim to address these weaknesses in the care cascade.
Method: A cluster, non-randomized intervention study where HRS are assigned to one of three arms Arm1: 4 HRS, viremia testing (GeneXpert) on-site, Arm 2: 2 HRS, blood draw on site, confirmatory testing (cAg) at a centralized laboratory, Arm 3 2 HRS, standard of care patients referred for testing at the treatment centre. Participants are eligible for the study if they tested anti-HCV positive on the same day and did not have prior confirmed diagnosis. The proportion of participants who completed each step in the HCV care cascade were compared across the three arms as well as the turn-around time of test results.
Results: Between May 2018 and November 2019, 1671 participants were enrolled (621 in Arm 1, 486 in Arm 2; 565 in Arm 3). Participants were predominantly male (95.4%), mean age was 44.0 (19–88) years and 79.1% were currently injecting drugs. 95% participants reported having taken an HIV test and of these 14 (0.84%) self-reported being HIV-positive. To date, 1517 participants have had a confirmatory viremia test done: 621 (100%) in Arm 1, 483 (99.4%) in Arm 2; 438 (77.5%) in Arm 3. Of those confirmed positive, treatment was initiated for 450 (87.0%) in Arm 1, 273 (70.9%) in Arm 2 and 345 (98.0%) in Arm 3. On average participants received their results the same day (<3 hours) in Arm 1, 21.5 days in Arm 2 and 18.6 days in Arm 3 from the time they had blood drawn for testing.
Conclusion: Confirmatory testing or blood draw on site at HRS showed improved retention of patients in the care cascade compared to referral of patients for blood collection. Moreover, the turnaround time was shortest when confirmatory testing was performed on site. These findings will facilitate scale up of decentralized HCV care for PWID in Georgia and globally.

SAT375

HBeAg seroconversion during treatment with peginterferon-alfa2a (PEG-IFN) is preceded by selection of hepatitis B virus basal core promoter and pre-core variants which are associated with decreased HBV replication

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Background and Aims: Variants in the basal core promoter (BCP, nt1743-1849) of the HBV genome (the mutations A1762T and G1764A [BCP++]) and a stop mutation at position 1896 (PC) in precore-region have been described to be associated with response to treatment with PEG-IFN. We have investigated the development of BCP++/PC variants during treatment with PEG-IFN.
Method: A total of 31 HBeAg positive(+) patients with (n = 19) or without (w/o, n = 12) subsequent HBeAg seroconversion (SC) matched by age, HBsAg levels and HBV genotype, who received PEG-IFN (180 μg/week) for 48 weeks in a prospective randomized study (Roche, WV16241), were retrospectively analyzed. In serum samples derived from baseline (BL), weeks 12, 24, 48 and 72 the HBV markers HBeAg, HBsAg, HBV DNA and HBV RNA were quantified. BCP and PC-stop regions were analyzed at all time points by direct sequencing of the region nt1690-2337 on either HBV DNA, or if HBV DNA was unavailable, on HBV RNA basis.
Results: At BL, 10/19 (52%) patients with subsequent HBeAg SC showed a BCP++ or PC stop mutation. Until the end of treatment all patients with HBeAg SC developed a mutation in the BCP/PC region. In contrast, only 2/12 (16%) patients w/o HBeAg SC showed a mutation before treatment, whereas additionally 5 patients developed a BCP/PC mutation during treatment (58%, $p = 0.003$). Analysis of the different HBV marker kinetics revealed a strong association of the occurrence of BCP or PC mutations and decreasing HBV RNA and HBeAg, but not HBsAg and HBV DNA levels during treatment. Thus, median HBV RNA levels decreased from 6.1 (0–8) log cp/mL before treatment to 3.3 (0–6.0) log cp/mL after 12 weeks of treatment and became (in median) subsequently undetectable in patients with HBeAg SC. Interestingly, in a few patients with persisting wildtype BCP/PC sequences (n = 3), HBV RNA levels remained unchanged in this patient group. Accordingly, patients w/o HBeAg SC who developed a BCP or PC mutation during treatment (n = 3/5), showed a strong decrease of HBV RNA levels from 7.6 (7.7–8.6) log cp/mL before treatment to 0.0 (0–4.3) log cp/mL after 48 weeks.
Conclusion: BCP and PC variants are being selected during PEG-IFN treatment, especially in patients with subsequent HBeAg SC. Irrespective of HBeAg SC, the occurrence of these variants leads to a decrease in HBV replication as measured by HBV RNA. The role of BCP/PC mutations in the process of HBeAg SC needs to be studied and our results to be confirmed in a larger population.

SAT376

Targeting hepatitis B virus with CRISPR/Cas9 approach

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Background and Aims: CHB infections persists mostly due to the lack of therapies that can effectively target the stable HBV covalently closed circular DNA (cccDNA) minichromosome. We used a CRISPR/Cas9 approach to target HBV genome and studied the fate of cccDNA after CRISPR/Cas9 gene editing.
Method: We set up a ribonucleoprotein (RNP) delivery system in de novo HBV infected HepG2 cells expressing the HBV receptor NTCP. RNP complex was delivered after infection was established to ensure targeting of cccDNA. HBV extracellular and intracellular parameters after Cas9 editing were analyzed. Southern blot analysis were performed to determine the presence of cccDNA and RNA-sequencing to determine if mutated cccDNA is transcriptionally active.
Results: Screening of different HBV-specific gRNAs, single or in combinations, showed that CRISPR/Cas9 can efficiently affect HBV replication. Depending on the target in the HBV genome, CRISPR/Cas9 led to degradation or mutations in total HBV DNA, both resulting in reduced viral transcripts. Besides a mild decrease in the amount of cccDNA, potentially due to degradation, we consistently observed the appearance of a smaller cccDNA species, by PCR, southern blot and RNA-seq indicating that this specie is transcriptionally active. Our results suggest that this "small cccDNA" is the product of double stranded breaks induced by Cas9 simultaneously in both target sites followed by repair of the bigger fragment. Following suppression of

HBV DNA replicative intermediate production by Nucleoside analogs (NAs) administrations, the addition of RNPs decreased cccDNA levels, suggesting that cccDNA is indeed directly targeted by the CRISPR/Cas9 complex.
Conclusion: Taken together, our results suggest that targeting HBV with CRISPR/Cas9 leads to mutation, cleavage and repair of cccDNA, and an effective synergy between NAs and CRISPR/Cas9 approaches. Notably, effects induced by Cas9 were sustainable indicating permanent changes in the HBV genome. Regardless of the truncation induced by a combination of gRNAs, the "small cccDNA" was still transcriptionally active and could potentially produce HBsAg. Further and longer-term in vivo studies would be necessary to determine efficient and irreversible gene editing.

SAT378
The correlations between HBV markers and HBV cccDNA in the patients during Na treatment

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Background and Aims: It is well known that HBV markers (HBV DNA, HBcrAg and HBsAg) in sera are linked to quantified HBV covalently closed circular (ccc) DNA in liver tissue. However, it remains unknown as to whether similar correlation exists in the patients during Nucleic acid analog (NA) treatment. The correlation between the HBV ccc DNA in liver tissue and serum HBV marker in the patients during NA treatment was investigated.
Method: 90 patients were included in this study. Intrahepatic HBV ccc DNA was quantified using specimen obtained by liver biopsy or from excised liver tissue in all patients between January 2012 and June 2018 (non-treatment 57, treatment 33). 1. Correlation between the HBV ccc DNA and serum HBV marker was investigated in all patients. 2. Correlation was investigated in 33 patients during NA treatment.
Results: A total of 90 patients were enrolled in this study. The median age was 57 year old. The median HBV ccc DNA levels was 3.4 log copies/μg (<1.7–5.3). The median levels of HBV markers in sera, namely HBV DNA, HBcrAg and HBsAg were 4.1 log copies/ml, 4.3 logU/ml and 3.23 logIU/ml, respectively. Ten cirrhotic cases were included and 19 patients had Gt B, 62 had HBV Gt C and 9 were unknown. 1. HBV markers were related to HBV ccc DNA in all patients. The correlation between HBcrAg and HBV ccc DNA was low in HBeAg negative patients (HBsAg, $r = 0.3989$, $p = 0.0012$; HBV DNA, $r = 0.7010$, $p < 0.001$; HBcrAg, $r = 0.6451$, $p < 0.001$). 2. The HBV markers related to HBV ccc DNA in the patients during NA treatment (HBsAg, $r = 0.4708$, $p = 0.0100$; HBV DNA, $r = 0.5052$, $p = 0.0052$; HBcrAg, $r = 0.6106$, $p < 0.001$). However, HBcrAg and HBsAg were not related to HBV ccc DNA in HBeAg negative (HBsAg, $r = 0.2892$, $p = 0.1917$; HBV DNA, $r = 0.1123$, $p = 0.6189$; HBcrAg, $r = 0.1418$, $p < 0.5290$) or HBV DNA negative patients during NA treatment (HBsAg, $r = 0.3223$, $p = 0.1435$; HBcrAg, $r = 0.2825$, $p = 0.2027$).
Conclusion: HBV DNA was related to HBV ccc DNA in the patients during NA treatment. However, no HBV marker in sera was related in HBeAg negative patients or HBV DNA negative patients in during NA treatment.

SAT379
Delineating HBV transcripts from integrated viral DNA using target enrichment and long read sequencing

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Background and Aims: Integration of Hepatitis B virus (HBV) DNA into the host genome is associated with the development hepatocellular carcinoma (HCC). Short read sequence analysis is limited to chimeric-read detection. To understand architecture, burden, and transcriptional activity of integrated HBV we developed a target enrichment assay for long-read sequencing. With this method, we can resolve full length integrations and differentiate transcripts from cccDNA or specific HBV integrations.
Method: DNA from 3 HCC cell lines PLC/PRF/5, HuH-1 and Hep3B was sheared to 7 kb fragments. Additionally, RNA from these cell lines and *in vitro* infected primary human hepatocytes (PHHs) was reverse transcribed to full length cDNA. DNA and cDNA libraries were barcoded for multiplexing, enriched using biotinylated 120 bp probes specific for HBV, then sequenced on a Pacific Biosciences Sequel II (PacBio).
Results: Target enrichment increased the frequency of HBV-aligning reads by >1000-fold. DNA sequencing captured entire integration events and, in several cases, greater than 1 kb of flanking host DNA in single reads. Many integrations only include portions of the HBV genome and appear transcriptionally silent. PLC/PRF/5 and HuH-1 cells both contain multiple integrations that intersect host chromosomal translocations. These chromosomal translocations are supported by spectral karyoptying.
Hep3B cells have a single transcriptionally active integration, but HuH-1 and PLC/PRF/5 cells produce three classes of HBV transcripts that: 1) fuse to host genes (e.g. *MVK*, *SNX15*), 2) read-through into the host genome distal to any known gene, or 3) exclude host sequences and terminate near the direct repeat region of HBV. Most transcripts start at Pre-S2 or S open reading frames. Class 1 and 2 transcripts appear to use the host poly(A) signal UAUAAA, while Class 3 transcripts are associated with a cryptic signal CAUAAA found in HBV. Many Class 3 transcripts in HuH-1 cells appear to be the same length, but single nucleotide polymorphism profiles show the transcripts come from two distinct integrations. Class 3 transcripts differ from all of the overlapping cccDNA-derived transcripts in PHHs which use a canonical 3′ end.
Conclusion: HBV-targeted long-read sequencing can distinguish three classes of HBV transcripts and assign HBV transcripts to specific integrations. This tool can provide a more accurate description of the burden and transcriptional activity of integrated HBV in patients.

SAT380
Prospective study of hepatitis B virus infection and its genotypes in the north-eastern India region

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Background and Aims: India has large burden of Hepatitis B virus infection with approximately 2–8% population being HBsAg positive, placing it intermediate HBV endemic zone. Hepatitis B virus genotypes have been associated with severity of liver disease, response to treatment and may conform to a geographical distribution. However, there is little information about HBV genotypes from North East India, which is host to the most indigenous tribes and a higher rate of drug abuse and HIV infection.
The aim of the study was to characterize HBV genotypes across various spectrums of liver diseases viz. acute viral hepatitis (AVH),

Fulminant hepatic failure (FHF), and chronic active hepatitis (CAH), Cirrhosis and hepatocellular carcinoma (HCC) prevailing in the North eastern states of India. We also tried to look for HBV mutants (Precore mutants, surface mutants, and X-gene mutants).

Method: The study was a prospective multicentric study based out of seven designated centers in six North East states of India from 2012 to 2015. 7464 different types of liver disease cases, 7432 prospective blood donors and 650 health care workers were screened for Hepatitis B virus infection. HBV DNA positive patients were genotyped and subjected to surface protein, precore and core mutation analysis and phylogenetic analysis was done.

Results: The prevalence of hepatitis B virus infection from all the centers was 9.9% (1550/15546). 48.9% (768/1550) cases were found to be HBV DNA positive. The most common genotype in north eastern region was found to be genotype D 74.2% (570/768) followed by genotype C 6.5% (50/768) followed by genotype A 4.4% (34/768) and genotype I 0.9% (7/768).

Conclusion: The study demonstrates the presence of multiple genotypes of HBV in the north-eastern states of India viz. genotypes A, C, D and I. However, genotype D has closest evolutionary distance with genotypes from the same region as well as from other parts of India while genotype C shows close evolutionary relatedness with previous sequences from the same region, Vietnam, Polynesia, South Korea and Philippines. Though the phylogenetic evolutionary study is incomplete due to use of limited numbers of reference sequences from other parts of the world, the overall scenario points towards a diverse mix-up and presence of multiple genotypes of HBV in the north eastern states.

SAT381

Hepatitis D virus entry, replication and assembly in stem cell-derived hepatocytes

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Background and Aims: The most physiological model for hepatitis D virus (HDV) infection is the primary human hepatocyte (PHH), yet their application is restricted by donor-to-donor variability and rapid ex vivo dedifferentiation. Reconstituting the HBV/HDV receptor, human sodium taurocholate cotransporting polypeptide (NTCP) renders hepatoma cells permissive for HDV infection but they partially resemble hepatocytes due to their transformed nature. Since stem-cell derived hepatocytes have recently been proposed as a cell culture model for HBV, we aimed at characterizing HDV infection in this new model.

Method: Hepatocyte-like cells (HLCs) were differentiated from human embryonic stem cell H9 line in 16 days using a modified protocol, and maintained in culture medium supplemented with oncostatin M and 1.5% dimethyl sulfoxide (DMSO). Differentiated HLCs were transduced with adeno-associated virus serotype 8 (AAV8) encoding NTCP or lentivirus encoding HBV envelope proteins, respectively. After HDV infection, the level of intracellular HDV RNA and antigen (HDAg) was measured by quantitative PCR and immunofluorescence. NTCP was stained by a validated antibody. Upon expression of HBV surface proteins, secreted HDV level was titrated, and its infectivity was determined by a reinfection assay.

Results: The HLCs expressed NTCP albeit at lower levels than NTCP-overexpressing hepatoma cells and allowed HDV permissiveness. HDV could be completely blocked by entry inhibitor Myrcludex B, suggesting NTCP-dependent entry. Upon AAV8-NTCP transduction, NTCP overexpression did not profoundly enhance HDV replication, indicating that NTCP induction was not a limiting factor. We observed increasing numbers of HDAg-positive cells in an inoculum-dependent manner in both HLCs and PHHs, although HDV replication was 10~20 fold weaker in HLCs compared to PHHs ($HDAg^+$ cells: 2.2% versus 21.1% in HLCs versus PHHs). HDV replication induced dozens- to hundreds-fold increase of multiple interferon-stimulated genes in PHHs, however low-replicating HDV in HLCs upregulated levels of only IFI27 and IFL44 genes by 3-fold, suggesting interferon-independent host restriction on HDV in HLCs. In long-term infection, we observed HDV replication up to 23 days and assembly in HLCs transduced with lentivirus expressing HBV envelopes. Although expression of genotype D secreted 2-fold less HBsAg compared to genotype B, both genotypes enveloped comparable amounts of HDV virions. The virions enveloped with genotype D led to more HDAg positive cells in the reinfection.

Conclusion: Altogether HLCs permit HDV entry, replication, and assembly in the presence of HBV envelopes, which provides an additional culture model in HDV study.

SAT382

Crispr/cas9-tailored hepatitis B-x protein knockdown inhibits cellular hyperplasia, invasion and tumorigenicity of HBV-infected hepatoma cells.

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Background and Aims: We have demonstrated previously, that Hepatitis B-X protein (HBx), a transactivator protein encoded in HBV genome plays a crucial role in inducing cancer stemness, invasion, metastasis and cellular transition. In this study, our aim was to design a novel HBx gene specific single guide RNA (sgRNA) with CRISPR/Cas9 system to evaluated its knock-down effects on HBx induced tumorigenic and functional properties of hepatoma cell *in vitro*.

Method: *In silico*, we designed sgRNA against HBx by CRISPOR web based tool with minimal off target activity, further cloned in non-viral eSpCas9-2A-Puro(PX459)V2.0 vector (HBx-CRISPR). *In vitro,* HepG2-2.15 (stable hepatoma cell line with a HBV expression) transfected with HBx-CRISPR or control vector (PX459). In another set of experiment, HepG2 cells transfected with pGFP-HBx used as HBx specific +ve control. To assess the effects of HBx knockdown, functional properties of hepatoma cells including proliferation, migration and invasion were studied in all the set of experiments by transwell migration, invasion and wound healing assays. 3D-spheroid culture assays were performed to study cancer stemness-properties in HBx knockdown and control cells.

Results: Our results showed that the HBx knockdown in the hepatoma cell line decreases HBx gene expression significantly (18 folds decreased, $p > 0.001$ Fig 1A). The HBx knockdown cells showed a markedly reduction in cell proliferation in comparison to cells transfected with the control vector (two folds) and pGFP-HBx (five folds). We observed significant decrease in tumorigenic properties - chemotaxis and invasion in the cells treated with HBx-CRISPR as compared to cells treated with control vector (migration $p > 0.05$) while in pGFP-HBx transfected cells, we observed significant augmentation in tumorigenecity (migration $p > 0.01$, invasion $p > 0.05$, Fig 1B-D). 3D spheroid cultures established that cells treated with HBx-CRISPR formed less number ($p > 0.01$, Fig1E,F) and smaller size ($p > 0.001$ Fig1E,G) of spheroids in culture as compared to cells treated with control vector, which confirms HBx-knockdown reduces stemnness property of hepatoma cells.

Conclusion: The study for the first time shows that targeting HBx by novel tailored CRISPR/Cas9 system effectively reduces the proliferation, invasion and stemness characteristics of hepatoma cells. This study represents an effective and evident non-viral therapeutic approach to control HBV-induced tumor progression.

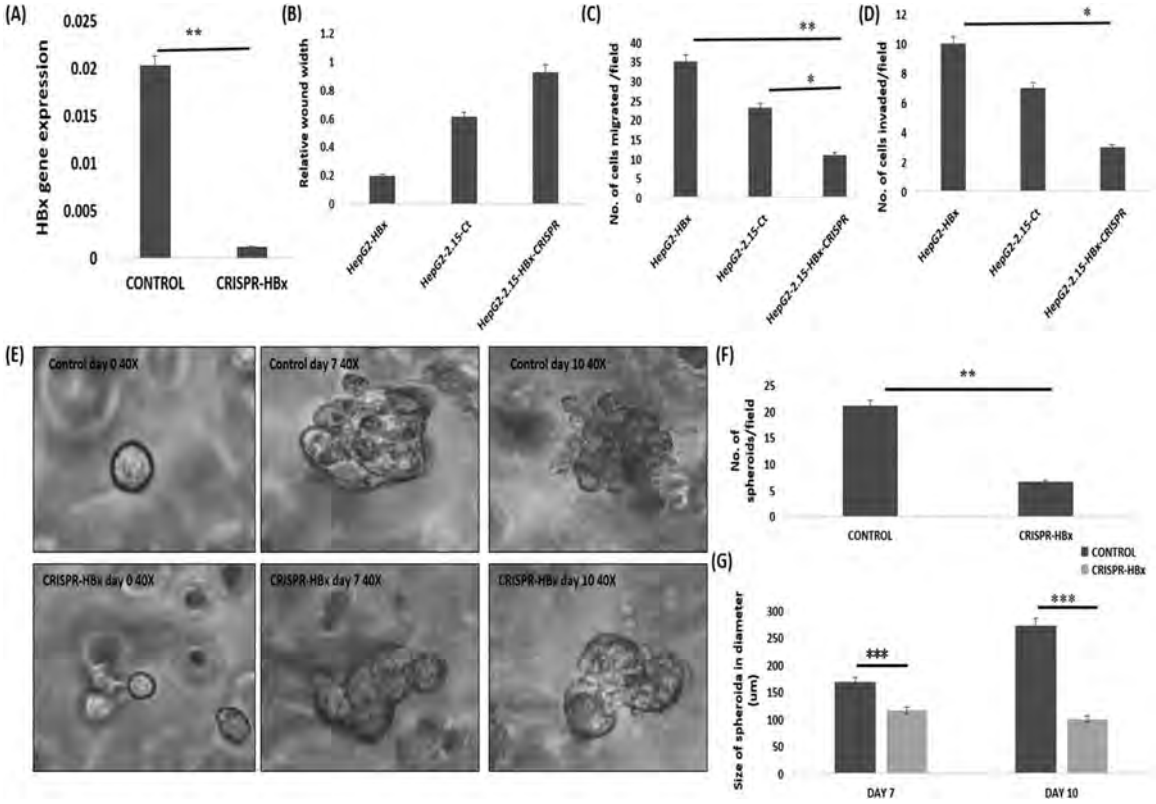

Figure: (abstract: SAT382): (A) Relative gene expression of HBx after transfected with HBx-CRISPR (B) Bar diagram showing relative wound width in HepG2-HBx, HepG2-2.15-Ct and HepG2-2.15-HBx-CRISPR (C,D) Chemotaxis and invasion assays depicting migration of hepatoma cells (E) Phase contrast images of spheroids on day 0, 7 and 10 (F,G) Bar diagram showing number of spheroids and size of spheroids in hepatoma cells. (**p > 0.01, ***p > 0.001).

SAT383

Cryptic HBV viremia in anti-HBC positive/HBsAg negative patients with HIV infection is frequently revealed by applying an ultrasensitive droplet digital PCR assay

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Background and Aims: Occult HBV infection (OBI) is frequent and associated with poor survival in the setting of HIV infection. Here, we investigate cryptic HBV replication and factors correlated with its detection in anti-HBc positive/HBsAg-negative HIV-infected patients by applying a highly-sensitive (HS) digital droplet (dd) PCR assay for serum HBV-DNA quantification.

Method: This study includes 81 anti-HBc-positive/HBsAg-negative patients with serum HBV-DNA <10 IU/ml by a commercial Real-Time PCR. All patients are HIV-infected, treated with an antiretroviral therapy including ≥1 anti-HBV drug: TAF/FTC (N = 37), TDF/FTC (N = 25), or LMV (N = 19) (median [IQR] duration: 35 [17–61] months). Serum HBV-DNA is quantified by an in-house HS-ddPCR (BioRad) whose linearity, reproducibility and sensitivity are assessed by testing serial dilutions with known concentration of HBV-DNA. Fujirebio assay is used to assess anti-HBc titer (proposed to infer cccDNA amount in the setting of OBI [Caviglia, 2018]). Factors correlated with the detection of cryptic viremia (serum HBV-DNA ≥1 IU/ml) are defined by Fisher exact test.

Results: ddPCR shows excellent linearity in the range of HBV-DNA from 1 to 10,000 IU/ml (R2 = 0.997), good intra- and inter-run reproducibility (coefficient of variation: 7.8% and 18.6%) and high sensitivity (limit of quantification: 1 IU/ml).

Overall, median (IQR) anti-HBc titer is 4.2 (2.4–11.6) COI. 30% of patients are isolated anti-HBc and 70% anti-HBc/anti-HBs positive (median [IQR] anti-HBs titer: 278 [90–957] mIU/ml). Median (IQR) HIV-RNA and CD4+ cell count are <20 (<20–38) copies/ml and 541 (331–727) cells/ul, respectively.

Notably, by ddPCR, cryptic HBV viremia is detected in 29.6% of patients with a median (IQR) HBV-DNA of 4 (1–15) IU/ml. No impact of different anti-HBV drugs on cryptic HBV viremia is observed (percentage of patients with serum HBV-DNA ≥1 IU/ml: 27% for TAF, 28% for TDF and 37% for LMV, p = 0.7). Moreover, a positive correlation is found between HBV-DNA and HIV-RNA (Rho: 0.26, p = 0.02).

By analyzing serological markers, anti-HBs <50 mIU/ml combined with anti-HBc >15 COI is predictive of cryptic HBV viremia (63% of patients with anti-HBs <50 mIU/ml + antiHBc >15 COI has HBV-DNA ≥1 IU/ml vs 26% without this combination, p = 0.046, OR: 4.7 [1.1–21.7]).

Conclusion: ddPCR is a valuable assay for detecting cryptic serum HBV-DNA in the setting of anti-HBc positive/HBsAg-negative patients with HIV infection. The integration of innovative serological and virological markers can help identifying patients with cryptic HBV replication, thus optimizing OBI diagnosis.

SAT384

Osteopontin drives HBV replication and HBV-driven fibrogenesis and represents a novel therapeutic target to achieve functional cure in chronic hepatitis B

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Background and Aims: New therapeutic options are urgently needed for chronic Hepatitis B (CHB). We evaluated the host-protein Osteopontin (OPN) as a novel therapeutic target to achieve functional cure in CHB and abrogate HBV-driven fibrogenesis.
Method: Liver biopsies from 91 CHB patients and plasma from 174 treatment (tx)-naïve and nucleos(t)ide analogue (NUC)-treated patients were collected to measure intrahepatic/ plasma OPN by immunohistochemistry/ ELISA. In-vitro, HBV-transfected HuH7 cells and HBV-infected (+) HepaRG were quantified for OPN by real-time (RT)-PCR and immunofluorescence (IF). We also developed an ex-vivo model of acute HBV infection with human precision-cut liver slices (PCLS). HepG2215 cells, HBV+HepaRG and HBV+PCLS were treated with recombinant (r)OPN and blocking OPN-specific aptamer (APT). Intrahepatic and secreted virion-bound HBV DNA, cccDNA and HBsAg were analysed by RT-PCR, digital droplet PCR and ELISA respectively. Primary human stellate cells (pHSCs) were treated with rOPN- and OPN APT-treated HBV+HepaRG culture media (HCM) and fibrosis markers were measured by RT-PCR/ IF.
Results: We observed a positive correlation between OPN levels and fibrosis severity in the liver and plasma of CHB patients ($r = 0.6$, $p < 0.0001$; $r = 0.27$, $p = 0.005$). Tx-naïve CHB patients with no fibrosis (F0) had higher OPN levels than NUC-treated CHB with suppressed viral load and healthy controls. OPN levels positively correlated with HBV viral load and ALT ($r = 0.57$, $p < 0.0001$; $r = 0.39$, $p = 0.0024$). NUC-treated CHB with fibrosis (F1-F4) also had reduced OPN compared to their paired untreated baseline sample. In-vitro, on-going viral replication in HuH7 and HepaRG increased OPN mRNA and protein expression significantly. Infection in PCLS was detected and remained stable for 7 days. Treatment with rOPN increased viral replication/ HBsAg in all 3 models of HBV infection and augmented cccDNA in HepaRG and PCLS. In contrast, viral replication, cccDNA and HBsAg levels were reduced by OPN-APT. Finally, fibrosis markers increased in pHSCs treated with rOPN-HCM and was inhibited by OPN APT-HCM.
Conclusion: This study is the first to report a dual role for OPN and shows its involvement in both HBV-replication and HBV-driven fibrosis. We show that OPN neutralisation can reduce HBsAg and cccDNA in in-vitro and ex-vivo models that recapitulate acute and chronic HBV infection and abrogate fibrogenic processes in human hepatic stellate cells. In summary, we reveal OPN as a new therapeutic strategy for CHB and HBV-driven fibrogenesis.

SAT385

Toll-like receptor 7 and 8 agonists as potent inhibitors of hepatitis delta virus infection

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Background and Aims: Worldwide an estimate of 257 million people is chronically infected with Hepatitis B virus (HBV) of which 5% are co-infected with the Hepatitis Delta virus (HDV). The course of infection leads to a severe liver inflammation which results in liver cirrhosis and the development of a hepatocellular carcinoma. So far, treatment options are limited to the administration of interferon alpha with response rates between 25 and 50%. Treatment of HBV-infected hepatocytes with Toll-like receptor (TLR) agonists showed a reduction of intracellular HVB DNA and HBeAg secretion. Since HDV is only found in association with an HBV infection it would be important to know if TLR-7 and TRL-8 agonists also affect HDV infection.
Method: Human hepatoma cell lines expressing NTCP (e.g. Huh-7, Hep3B) were infected with cell culture derived HDV and either directly treated with different concentrations of TLR-7 or TLR-8 agonists or indirectly, using supernatant of TLR-7 or TLR-8 stimulated peripheral blood mononuclear cells (PBMCs). The antiviral effect was measured by immunofluorescence staining against HDV or by quantitative RT-PCR. Mechanistically, induction of interferon-stimulated genes (ISGs) as well as secretion of chemokines and cytokines were evaluated by a quantitative SYBR Green based RT-PCR or Luminex Assay, respectively.
Results: Direct treatment of infected hepatoma cells had no effect on viral replication while indirect treatment with stimulated PBMCs supernatant significantly inhibited HDV infectivity. We further

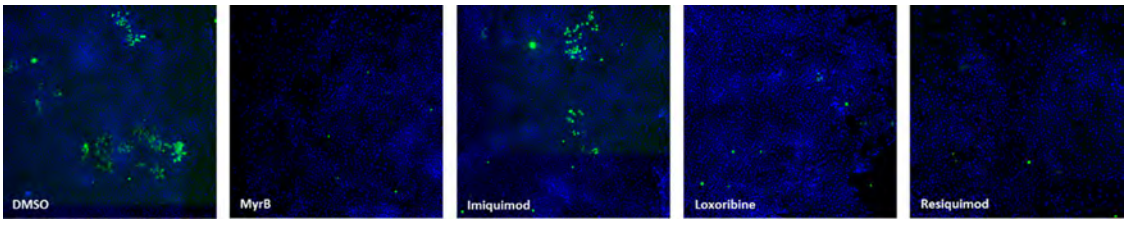

Figure: (abstract: SAT385)

observed that the TLR-7/8 agonist resiquimod was the strongest inhibitor compared to the TLR-7 agonists imiquimod and loxoribine. Furthermore, resiquimod was the most potent inducer of cytokines with IL-6, IL-8 and ITAC-1 significantly increased under TRL treatment. A comparable effect was observed for ISG induction (MDA5, MxA, RSAD2, ISG15, OAS1 and RIG-I). In addition, IFN-α induction was determined and found to be five times more increased by resiquimod than imiquimod or loxoribine. Time kinetic revealed that IFN-α peaked at 4 hours under resiquimod treatment while induction is delayed for imiquimod and loxoribine (peaked at 8 h post treatment).
Conclusion: In conclusion, TLR-7 and TLR-8 agonists showed potent anti-HDV effects in vitro and were able to induce various cytokines in stimulated PBMCs. Together with the induction of type I IFN and ISGs it led to an antiviral state of the cell to control HDV infection.

SAT386

Viral compartmentalization and carcinogenesis at single-cell level in HBV-induced hepatocellular carcinoma

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Background and Aims: Chronic hepatitis B virus (HBV) infection is a major cause of hepatocellular carcinoma (HCC) world-wide. HCC can raise despite low HBV load in non-cirrhotic livers. Molecular mechanisms of virus-cancer interactions and hepatocarcinogenesis are still partially understood. Here, we investigated HBV-host cell interactions in patient-derived HCC using deep single-cell sequencing.
Method: Combining two deep single-cell RNA-sequencing (scRNA-seq) approaches, mCEL-Seq2 and Smart-Seq2, we analyzed HCC cells and tumor microenvironment from patients with low HBV viral load. The Smart-Seq2 protocol allowed for deep full transcript sequencing including the analysis of putative viral integration sites of the host genome.
Results: Computational analyses of gene expression revealed a marked heterogeneity of the HCC. Analyses of virus-induced host responses identified previously undiscovered pathways mediating viral carcinogenesis, including a marked correlation of HBV load and the oncogene SERTAD2. Mapping of fused HBV-host cell transcripts unraveled integration sites in individual cancer cells. The combination of integration analysis and RNA-expression profiles allowed the tracing of cancer development and identification of previously unknown genes implicated in the hepatocarcinogenesis and associated with long-term patients' prognosis. HBV-RNA load was not uniformly distributed across cancer subclones being higher in more differentiated cells and highlighting the fundamental role of HCC in the early phases of carcinogenesis and tumor progression.

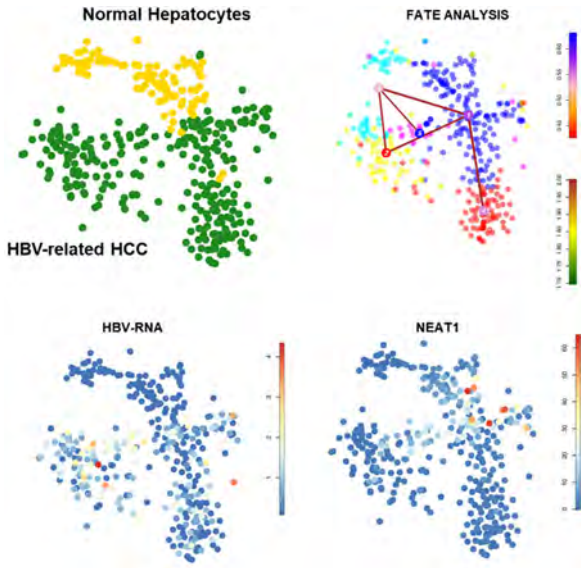

Figure: ScRNA-seq unravels HBV compartmentalization, traces HCC development, dissects the hepatocarcinogenesis and discovers new genes implicated in this process. Data of cancer cells from HBV-induced HCC and normal hepatocytes were integrated and the tumor development was traced (Fate Analysis). HBV-RNA is not uniformly distributed among cancer cells and is higher in more differentiated cells. Gene associated with tumor development such as NEAT1 were also identified.

Conclusion: ScRNA-seq unravels heterogeneity and compartmentalization of both, virus and cancer. The perturbation of gene expression mediating carcinogenesis in cells with low viral RNA levels highlights the importance of curing HBV chronic infection to eliminate both HCC risk and tumor progression. The marked tumor heterogeneity suggests that combination therapies targeting multiple drivers are required for HCC chemotherapeutic approaches.

SAT387

Pangenotypic therapies glecaprevir-pibrentasvir (G-P) and sofosbuvir-velpatasvir-voxilaprevir (S-V-V) after failure with interferon (IFN)-free direct-acting antiviral (DAA) treatment for hepatitis C

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Background and Aims: Despite the remarkable effectiveness of IFN-free DAA treatment in real-world HCV care, treatment failures remain a challenge in disease eradication. Here, we examine outcomes with G-P or S-V-V after DAA failure/relapse.
Method: Inclusion: patients who failed or relapsed following IFN-free DAA therapy and were subsequently treated with G-P (n = 55) or S-V-V (n = 176) between July 2017 and Dec 2018. Data were collected electronically from providers and specialty pharmacies. Variable comparisons were via Exact tests with subsequent z-tests of column proportions. Significantly different variables were used in a logistic regression to generate propensity scores for 1-1 matching without replacement with G-P as the test group. Therapy duration was not included in matching due to sample limitations.
Results: In comparison to S-V-V, the G-P group had a higher percentage of baseline eGFR <30 ml/min (8% v. 1%, p = 0.015), genotype (GT) 2 HCV (9% v 2%, p = 0.040), hypertension (60% v. 42%, p = 0.016), and care at academic centers (42% v. 26%, p = 0.021). G-P

and S-V-V treatment groups were not significantly different for age, gender, insurance, ribavirin, anxiety, depression, diabetes, HCC, HIV, or HBV and had characteristics of GT1 (82% G-P v. 78% S-V-V, p = 0 0.589) and baseline FIB4 >3.25 (37% G-P v. 38% S-V-V, p = 0.651). Therapy duration for G-P was 16 weeks (69%), 12 weeks (16%), and 8 weeks (15%); for S-V-V, 99% patients received 12 weeks (p < 0.001). Prior therapy was mostly ledipasvir-sofosbuvir (L-S) for both G-P (64%) and S-V-V (58%). SVR rates were significantly lower for G-P compared to S-V-V for both intent to treat (ITT, 84% v. 94%, p = 0.017) and per protocol (PP, 85% v. 98%, p < 0.001) populations. After propensity score matching, treatment groups (n = 39 pairs) significantly differed only by therapy duration (G-P 69% 16 weeks, 15% 12 weeks, 15% 8 weeks v. S-V-V 100% 12 weeks, p < 0.001) and had the following characteristics: 95% GT1, 5% GT 3, 100% eGFR>30 ml/min, 33% (G-P) to 36% (S-V-V) FIB4 >3.25,and prior therapy predominantly L-S (80%). In the matched sample, SVR rates were significantly lower for G-P compared to S-V-V for ITT (85% v. 97%, p = 0.048) and PP (85% v. 100%, p = 0.012).

Conclusion: In patients with prior DAA failure/relapse, significantly higher ITT and PP SVR rates were observed with S-V-V compared to G-P both before and after adjustment for clinical differences.

SAT388

A novel intrahepatic restriction factor, HMGA1, contributes to hepatitis B virus (HBV) replication in immune tolerant phase, serving as an anti-HBV target

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Background and Aims: In clinic, hepatitis B virus (HBV) replicates at much higher levels in immune tolerant (IT) phase than in inactive carrier (IC) phase. Since the immune responses are similarly comparable between the two phases, intrahepatic host restriction factors (HRFs) are generally accepted to play an important role in HBV gene expression and replication. Previously, we identified a serial of differentially expressed intrahepatic HRFs based on RNA sequencing of liver tissues from the two phases. Identification of functional HRFs contributes to elucidating the virological differences between the two phases, and more importantly, to developing the novel anti-viral candidates for treating chronic hepatitis B (CHB). In this work, we focused on HMGA1, whose mRNA levels are higher in IT phase than in IC phase, and explored the reasons for differential expression of HMGA1, as well as the mechanism by which HMGA1 regulates HBV.
Method: Immunohistochemistry analysis of HMGA1 expression in liver tissues; Serial cell models were used to analyze whether HMGA1 regulates HBV; Co/Chromatin-immunoprecipitation (Co-IP/ChIP) was performed to analyze the interaction between protein/DNA and protein. HBV chronic cccDNA mouse model were used for evaluation of antiviral effects based on gene therapy.
Results: HMGA1 protein levels in IT phase are much higher than in IC phase; HMGA1 promotes HBV gene expression and replication via the activation of HBV core promoter (Cp); The Cp activation depends on the specific binding of transcription complex, in which HMGA1 recruits protein A and B, to a novel cis-element in Cp; Sp1 protein upregulates HMGA1 at transcriptional levels via the recruitment of hepatitis B X (HBx) protein to HMGA1 promoter; Lastly, knockdown of HMGA1 expression significantly cleared HBV persistence in cccDNA mouse model.

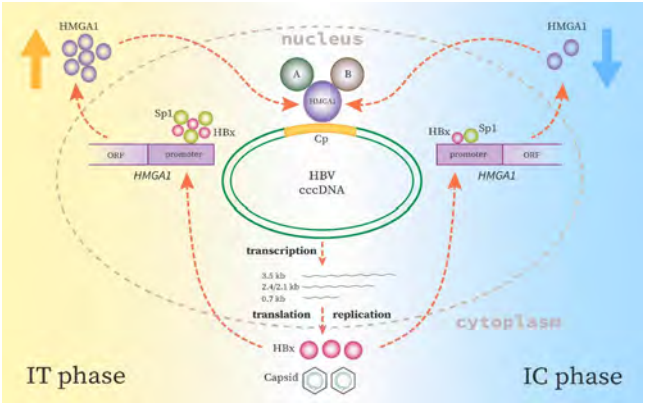

Figure: HMGA1 up-regulates HBV replication via a positive feedback loop. IT: immune tolerant; IC: inactive carrier; Cp: core promoter.

Conclusion: HMGA1 is a key factor to sustain the higher HBV replication in IT phase, and on the other hand, HBx upregulates HMGA1 in a positive feedback manner.

SAT389

Multivariant surface quasispecies in a hepatitis B virus chronically infected individual with concomitant and continually positive surface antigen and anti-HBS biomarkers

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Background and Aims: Coexistence of hepatitis B virus (HBV) surface antigen (HBsAg) and antibodies (anti-HBs) can be found in 2.3–5.2% of chronically HBV infected individuals. Recent reports have indicated that the presence of both biomarkers is associated with high risk of hepatocellular carcinoma (HCC). However, previous studies with clinical samples presenting both biomarkers have demonstrated that the presence of variants in the HBsAg surface (S) gene and anti-HBs subtype-nonspecific can contribute to coexistence of these two biomarkers in chronic HBV infection (CHB).
Method: Herein, we analyzed HBsAg variants in a clinical sample from a 43-years old female CHB individual, with prolonged (>7 years) coexistence of HBsAg and anti-HBs, HBeAg negative, and treatment with TDF. Total DNA was purified from plasma and HBV DNA amplified. We used next generation sequencing (NGS) and a novel HBV-specific assembly/machine-learning tool for quasispecies analysis of the S gene (GATACA Assembly Tool, GAT).
Results: We determined the frequency of 18 site variants in the Surface gene (Table 1). Interestingly, variants Y100S and L127P occurred together in the same haplotypes and eight sites studied presented a variant with stop codon. We found several quasispecies of a same amino acid variation in the variants' pool within this clinical sample. In addition, we demonstrated that defective HBsAg variants can coexist with the wild type and other functional variants. Seven site variants were found in the "a" determinant region of HBsAg that could explain its persistence despite the presence of anti-HBs.

Table 1: Surface gene sites with amino acid identified with GAT

S gene site	Stop codons	AA variants
Y100stop/Y*/N*/S/F/H/C/N	1	7
S114T*/S*/I/P/K/T*/Q	0	6
P120P*/T*/S*/A*/L*/R*/G/H	0	7
C121STOP*/C*/F/L/S*/R/V/T	1	7
C123T*/P/S/N/A	0	5
L127P*/T*/H*/S	0	4
Q129Q*/P*/H/K/T/S/Y	0	7
G130G*/V*/E/D/A*/R*/C*/S/P*/F/STOP	1	10
M133L*/T*/I*/Q/F/K	0	6
F134F*/S*/Y*/C/L*	0	4
D144D*/A*/N/T	0	3
G145G*/STOP/V	1	2
E164E*/D*/G*/A*/R*/V*	0	5
W172L/R*/C*/G/S/STOP	1	7
W182L/R*/C*/G/S/STOP	1	7
I915I*/M/L*/V*/T*/R*/K*	0	6
W196L*/C*/F*/R/G/S/V/STOP	1	8
L216L*/V*/S/STOP*	1	3

*NOTE amino acid with different nucleotides.

Conclusion: Considering that HBsAg S gene is a potential target for antiviral development and HBsAg seroconversion is a potential outcome for functional cure, understanding the dynamics of these variants can help to identify strategies of use for the novel direct-acting antiviral agents.

SAT390

Evaluation of the introduction of hepatitis C core antigen as a routine test to detect viraemia among patients with anti-HCV antibodies

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Background and Aims: Hepatitis C core antigen (Ag) is recommended as an alternative to RNA testing to diagnose current hepatitis C (HCV) infection. Published data has assessed the performance of Ag testing using analysis of cross sectional cohorts. We aimed to assess the performance of Ag testing when introduced as routine to the West of Scotland Specialist Virology Centre.

Method: HCV antibody positive serum samples from June '11, when reflex Ag testing using the Abbott Architect assay became routine, to December '17 were identified from the Scottish HCV test database. Positive Ag results were reported as showing current infection, negative samples as indicating the absence of infection, but recommending an RNA test to confirm. This was either with a further sample, or by request on the index sample. We identified samples where on request RNA testing was performed. Samples with insufficient serum, or for which the Ag test was equivocal, were excluded. For the remainder, the sensitivity and specificity of HCV Ag as a diagnostic tool was assessed using HCV RNA PCR as reference. Multivariate analysis was performed to identify factors associated with a false negative test.

Results: 877/4693 (18.7%) reflex Ag samples had on request PCR testing. 92 samples were excluded (58 insufficient serum, 34 equivocal Ag). 246/775 (31.3%) samples were Ag negative, and 539 (68.7%) positive. Baseline characteristics are shown below. 244/302 samples were RNA and Ag positive (sensitivity 80.8%, 95% CI 76.4–85.2%) whilst 472/473 samples were RNA and Ag negative (specificity 99.8%, 95% CI 99.4–100.2%). The odds of a false negative were raised for genotype 3 (OR = 3.44, 95% CI: 1.15–10.3) and were lowered with older age (OR = 0.93, 95% CI: 0.88–0.98 per year) and viral load (OR = 0.12, 95% CI: 0.07–0.21 per log10 IU/ml2). For samples with known genotype, all (11/11) false negative results with a viral load >3000 iu/ml occurred in genotype 3 infection.

Baseline characteristics	Number (%)
Male	503 (64%)
Female	282 (36%)
Median Age	44 (range 21–90)
Ethnicity	
Unknown	40 (5.1%)
Non-UK indigenous	63 (8.5%)
White	682 (86.9%)
HCV genotype	
Untested	5 (0.6%)
Unknown	489 (62.3%)
1	107 (13.6%)
2	10 (1.3%)
3	173 (22.0%)
4	<5
Co-infection	
HBV	60 (7.6%)
HIV	42 (5.3%)
Cirrhosis	
Yes	97 (12.3%)
No	682 (87.7%)
Methadone	
Unknown	491 (62.5%)
Yes	172 (21.9%)
No	122 (15.5%)
Transmission route	
Unknown	505 (64.3%)
Person who injects drugs (PWID)	249 (31.7%)
Contaminated blood	18 (2.3%)
Other	13 (1.6%)
HCV RNA (log_{10} IU/mL)	4.24 (1.08–7.01)
HCV Ag	
Positive	246 (31.3%)
Negative	539 (68.7%)

Conclusion: In routine use reflex Ag testing is highly specific, but lacks adequate sensitivity. In addition to known limitations at detecting low level viraemia, the Ag assay failed to detect higher level viraemia amongst a number of genotype 3 samples. These findings have implications for the routine introduction of Ag testing, particularly where genotype 3 is prevalent.

SAT391

Virologic causes for DAA treatment failure of chronic hepatitis C

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Background and Aims: Chronic hepatitis C (CHC) is common in Taiwan, as about 4% of population are positive for anti-HCV Ab. Among them, around 70% carry HCV RNA, therefore about 500,000 cases are CHC patients. The Bureau of National Health Insurance has started to reimburse DAAs (direct-acting antiviral agents) since 2017. Preliminary data from Hepatitis C Flagship Project Office showed an HCV cure rate of 97%, meaning that there are still 2–3% of patients who fail to clear HCV despite completing the treatment. In order to understand the causes of treatment failure in Taiwan, it is essential to conduct a clinical and virologic study of these DAA failure patients.
Method: Through collaboration with several hospitals and clinics nationwide, we recruited 40 DAA failure patients. These patients received at least four-week treatment of DAA therapy. Clinical information as well as serum samples were obtained after informed consent. We established polymerase chain reaction (PCR) platform for NS3/4A, NS5A and NS5B, and then identified mutated RAS (resistance-associated substitution) by population sequencing.
Results: In these 40 patients, only one patient did not complete treatment due to hyperbilirubinemia. Sixteen patients had genotype 1b infection, twelve had genotype 2, and two had genotype 3.
Till now, we completed RAS (resistance associated substitution) analysis for 21 patients among these 40 patients. Eight cases were found to have no known RAS according to its genotype and DAA regimen, and the rest 13 cases were found to have at least one mutated RAS. Y93 in NS5A was the most RAS, and its frequency of mutation (91%) was significantly higher than that in HCV database (14%). The frequency of mutation of Y56 in NS3 and L31 in NS5A were also higher than those in HCV database. On the other hand, the frequency of mutation of D168 in NS3 and L159 as well as C316 in NS5B were not higher than those in HCV database. Furthermore, two cases were noted with post-DAA HCV genotypes that were different from the baseline genotypes, suggesting initial mixed infections or a reinfection.
Conclusion: Our study suggests that known RASs are the major virologic cause for treatment failure. Those without known RASs warrant further investigation in order to propose appropriate rescue therapies.

SAT392

Impact of direct antiviral agents (DAAs) on the HBV virologic profile in HCV+ but HBsAg– and HBcAb+ patients

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Background and Aims: We have published a case of HBV viral reactivation during DAA treatment in an HIV/HCV+ and HBsAg- patient (1). Few data are available in patients with a cured hepatitis B profile. The purpose of this study was to evaluate the impact of DAAs treatment on the HBV profile in this category of patients.
Method: From March 2015 to October 2016, 60 HCV + patients (44 M, 16 F), median age 58 years, including 21 cirrhotic patients were treated with DAAs. All of these patients were HBsAg- and HBcAb+. 25 patients were also anti HBsAb +. Before treatment, 2 patients had a detectable but unquantifiable HBV viral load (VL). One patient was co-infected with HIV/HCV. The combinations of DAAs used were SOF + DCV, SOF + LDV, SOF + SMV, 2D, 3D, ±ribavirin. The duration of the treatments was between 12 and 24 weeks according to the recommendations. A virological assessment of HCV and HBV was performed every month for 3 months, then at the end of treatment, 3 months and 6 months later.
Results: A patient was lost of follow up at week 8. In ITT, the SVR12 was 98.3%, and 100% in per protocol. Six patients (10%) had HBV quantifiable VL during follow-up. The following table summarizes the evolution of HBV viral loads during the study.
Among the 6 patients who had their HBV VL detectable, transaminases remained in the normal values in 4 patients. In 2 patients, there was a slight elevation of transaminases at the time of HBV VL detection: ASAT at 1.3 times the upper normal limit for one and ALAT at 1.6 times the upper normal limit for the second. The level of HBsAb increased in 2 of 6 patients at the end of follow-up.
Conclusion: The detection of HBV VL in HCV+ patients with HBsAg-, but HBcAb+ is frequent (10%) during DAAs treatment. However, the elevation of HBV VL remains low, with no clinico-biological consequences. Virological HBV monitoring is advised at the end of treatment.

Reference

(1) Monte A et al. *J Clin Virol*. 2016 May; 78: 27–30.

SAT393

Usefulness of HEV antigen determination in the diagnosis of acute hepatitis E

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Background and Aims: The diagnosis of acute hepatitis E (AHE) is based in the presence of RNA-HEV, with or without antiHEV-IgM. However, due to the short duration of viremia, antiHEV-IgM presence in a patient with acute hepatitis (AH) is used as diagnostic criteria, despite its limitations. Aim: To know the HEVAg behaviour in a series of patients with AH.
Method: HEVAg was determined in 27 patients diagnosed of AHE (antiHEV-IgM positive), in 10 patients with acute hepatitis A (AHA), antiHAV-IgM positive, and in 10 patients with AH of probable toxic

Table: (abstract: SAT392)

		Follow up (FU) of HBV viral load (UI/ml)					
Patients	HBsAb (UI/l) Baseline	Baseline	Week 4	Week 8	End of treament (Week 12 or week 24)	FU week 12	FU week 24
1	15	Undetectable	<10	<10	<10	18	<10
2	Negative	<10	14	25	25	Undetectable	<10
3	Negative	Undetectable	Undetectable	Undetectable	Undetectable	25	ND
4	Negative	Undetectable	ND	ND	18	<10	15
5	Negative	<10	32	53	<10	<10	22
6	Negative	Undetectable	Undetectable	Undetectable	16	Undetectable	Undetectable

<10: detectable but unquantifiable, ND: not done.

origin (TAH). The determination was made in the basal serum in all cases and 3 months later in 14 patients from the AHE group. The diagnosis of AH was based in ALT >5× ULN. HEVAg was determined by ELISA (Wantai, China), as well as antiHEV-IgM (DiaPro, Italy). RNA-HEV determination was made by RT-PCR.
Results: Among patients with AHE, 89% men, age 57 years (47–65), 7 (26%) had been transplanted. Hepatitis was icteric in 52%, severe in 18%, ALT 1.294 IU/ml (554–2967), bilirrubin 4,2 mg/dl (1,6–10,6) and 5 (18%), all transplanted, evolved to chronicity,. RNA-HEV was positive in 15/27 (55,5%) and HEVAg in 24/27 (89%). All samples RNA-HEV positive were HEVAg positive. In transplanted patients RNA-HEV was positive in 57% and HEVAg in 100%. The 3 antiHEV-IgM positive/HEVAg negative patients had lower ALT levels than those HEVAg positive (582 vs 1526) and more days from symptoms beginning to the analysis (6 vs 2). In the sample obtained 3 months after diagnosis, antiHEV-IgM was positive in 16/17 (94%) cases and HEVAg in 3/14 (21%), all evolved to chronicity. Positivity at 3 months in patients with self-limited infection was 99% for antiHEV-IgM and 0% for HEVAg. Patients with AHA were all men, 45 years (28–48), all icteric, ALT 2806 IU/ml (1936–2806) and bilirrubin 6,3 mg/dl (4,8–11). HEVAg was negative in all of them. Patients with TAH were 70% women, 55 years (45–63), 60% icteric, ALT 1754 IU/ml (900–1555) and bilirrubin 6,3 mg/dl (0,7–8,4). All were HEVAg negative.
Conclusion: HEVAg is present at diagnosis of AHE antiHEV-IgM positive in a much higher proportion than RHA-HEV, and in all RNA-HEV positive cases, so it should replace RNA-HEV in the AHE diagnosis. Antigenemia duration is lower than antiHEV-IgM; it provides advantages in the diagnosis of acute infection but could also lead to some miss diagnostic cases. Accordingly, HEVAg should be incorporated together with antiHEV-IgM to the serological profile for the etiological diagnosis of acute hepatitis.

SAT394

Hepatitis V virus (HBV) cccDNA mini-chromosome transposase-accessible chromatin by atac-sec in infected primary human hepatocytes (PHHs)

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Background and Aims: Transcriptional activation in eukaryotic cells has been tightly linked with disruption of nucleosome organization at open or accessible genomic sites of remodeled chromatin. Increasing evidence indicate that epigenetic modifications (cccDNA-bound histones post-translational modifications and cccDNA CPG islands methylation) determine the chromatin accessibility and the transcriptional activity of the cccDNA. Recent studies, using cccDNA CHIP-seq on HBV in-vitro infection models and liver biopsies, have confirmed that the acetylation of cccDNA-bound histones and the histone mark H3K4me3 are associated with high viral replication while the hypoacetylation and the repressive mark H3K4me3 translate into lower cccDNA transcription levels.
Methods: We used ATAC-seq (assay for transposase-accessible chromatin followed by high throughput sequencing) to probe open chromatin and detect early changes in cccDNA chromatin accessibility in HBV-infected human primary hepatocytes (PHHs). ATAC-Sec reads are aligned to the HBV genotype D genome (NCBI Reference: NC_003977.2) to generate cccDNA ATAC-seq profiles in HBV-infected PHHs 2 hours, 24 hours and 72 hours post-infection.
Results: We have previously shown that after HBV infection an increasing number of genomic sites change their chromatin accessibility over time with a prevalence of more open, potentially transcriptionally active regions, indicating that HBV infection impacts on host cells chromatin landscape and transcription. The alignment of ATAC-seq and RNA-seq reads to the HBV genome showed that cccDNA chromatin accessibility increases over time after infection with a well-defined profile 72 hours post-infection, when cccDNA is fully transcribed and pgRNA and preC 3.5 kb RNA species are detected in the RNA-seq. The ATAC-seq profile at 72 hours post-infection shows 2 major regions of high chromatin accessibility (CA1 and CA2). The CA1 region overlap a peak of Pol2 recruitment and nucleosomes with highly acetylated H3K27 that are reflected in the accessibility profile of CA1.
Discussion: Altogether these results show that the cccDNA ATAC-Seq allows to study the dynamics of cccDNA chromatin accessibility. cccDNA ATAC-seq may represent a new, rapid and potentially down-scalable, tool to evaluate cccDNA chromatin accessibility, how it relates to cccDNA transcription and how is modified by cytokines, immune responses, HBV direct antiviral agents (DAAs) and host targeting agents (HTAs).

SAT395

Resistance monitoring data from treatment-naive chronic HBV infected patients treated for 28 days with a new class a core protein allosteric modulator RO7049389 monotherapy

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Background and Aims: RO7049389 is a small molecule, Class A HBV core protein allosteric modulator being developed for the treatment of chronic hepatitis B. In a Phase Ib clinical study (NCT02952924), treatment-naive chronic HBV infected HBeAg-positive and -negative patients received 4 weeks oral administration of RO7049389 or placebo (200 mg to 1000 mg daily). Potent antiviral effects were observed and no subject experienced virologic breakthrough. Here, we present the resistance monitoring data of this study.
Methods: A near full-length HBV genome was amplified and underwent next generation sequencing using HBV DNA extracted from the baseline samples of all 37 patients and from the end of treatment (EoT, day 28) and subsequent last follow-up visit (LFU) samples of all 22 patients who had a quantifiable HBV DNA (>20 IU/mL) at EoT. The mutations in each sample were determined by comparing with the HBV reference sequence (HBV genotype A, NCBI ID X02763). The analyses focused on amino acid substitutions in the core protein, especially the 24 positions located within the putative compound-binding pocket suggested by cocrystal structures. The impact of mutations on the susceptibility to RO7049389 was assessed in a transient transfection assay using corresponding point-mutants.
Results: A total of 71 samples, 34 baseline (28 active: 6 placebo), 16 EoT (11 active: 5 placebo), and 21 LFU (17 active: 4 placebo), were successfully amplified and sequenced. Among them, only 5 samples from 3 patients contained amino acid substitutions of >5% frequency in any of the 24 amino acids of the putative compound-binding pocket. One patient (active) harbored 99.9% T109C at baseline, which decreased to 67.8% at LFU. The second patient (placebo) harbored 15.8% T109M at baseline, which increased to 99.8% at EoT. The LFU sample of this patient failed amplification. The third patient (active) harbored 8.0% I105 V at baseline and HBV DNA went below 20 IU/mL at EoT. In vitro assays with the corresponding point-mutants showed that T109C and I105 V did not confer resistance to RO7049389, while

T109M led to reduced susceptibility to RO7049389 (5.4 fold change in EC50), at the cost of reduced replication capacity (22% of the wild type). The reason why T109M was enriched during placebo treatment remains unclear.

Conclusions: In this study, a low occurrence of polymorphisms within the 24 amino acids in the putative binding pocket of RO7049389 was observed in all sequenced samples. Baseline polymorphisms known to reduce RO7049389 activity were observed in only 1 of the 34 (3%) patients with baseline sequence data, as this was a placebo-treated patient, no conclusion on reduced in vivo susceptibility can be drawn. No mutations known to reduce RO7049389 activity in vitro emerged or were enriched after 28 days of treatment, which is consistent with the robust decline in plasma HBV DNA among all patients who received RO7049389 monotherapy.

SAT396

Developing a sensitive HBV genotyping assay for HBV DNA suppressed patients using both DNA and RNA sequencing

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Background and Aims: Hepatitis B virus (HBV) genotypes impact treatment outcomes and disease progression. Due to limitations of current genotyping methods in patients with low HBV viral load, here we have developed a more sensitive assay for determining HBV genotype in HBV DNA suppressed patients using DNA and RNA sequencing followed by phylogenetic analysis.

Table 1: Success rate for amplification and genotyping of samples

Genotype[a]	Success rate for amplification and genotyping, n/N (%)
A	8/8 (100%)
B	8/8 (100%)
C	7/8 (87.5%)
D	8/8 (100%)
E	7/7 (100%)
F	9/10 (90%)
G	1/1 (100%)
H	5/5 (100%)
Total	53/55 (96.4%)

[a]Historical genotype was determined by INNO-LiPA or RT sequence (1–344 aa) from baseline sample.

Method: Fifty-five serum samples from 55 chronic hepatitis B patients (HBeAg–, n = 20; HBeAg+, n = 35) across genotypes A to H with long-term tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF) treatment from Gilead clinical studies were collected. All samples had undetectable HBV DNA (HBV DNA <29 IU/mL by COBAS TaqMan Assay). Total nucleic acid was extracted and a 341 bp amplicon located at HBV S gene overlapping with reverse transcriptase domain of polymerase (RT/pol) was amplified from both viral DNA and RNA via RT-nested PCR followed by population sequencing. HBV genotype was determined by phylogenetic analysis.

Results: The assay successfully amplified HBV S/RT gene from 53 of 55 (96.4%; HBeAg-, n = 19; HBeAg+, n = 34) patient serum samples with HBV DNA <29 IU/mL across GT A to H using both DNA and RNA sequencing. Phylogenetic analysis demonstrated the genotypes of all the 53 PCR positive samples matched the historical genotypes determined by INNO-LiPA or RT sequence (1–344 amino acid) from the corresponding baseline samples (Table 1). The majority of the samples (61%) were from patients that had been on suppressive therapy for 3 years. In two cases, we were able to genotype patients that maintained HBV DNA undetectable status for >4.5 years.

Conclusion: A sensitive genotyping assay for HBV DNA suppressed patients using both HBV DNA and RNA sequencing and phylogenetic analysis can accurately determine HBV genotype irrespective of baseline genotype, HBeAg status, or duration of viral suppression. The ability to determine genotype in virally-suppressed patients may facilitate the evaluation of novel treatment agents for HBV in this patient population.

SAT398

Impact of antiviral therapy for blocking mother-to-child transmission on virus quasispecies in pregnant women with chronic HBV infection

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Background and Aims: To explore the effect of short-course antiviral therapy for blocking mother-to-child transmission (MTCT) of HBV during pregnancy on the quasispecies heterogeneity of the HBV reverse transcriptase (RT) region and the correlation between the evolution of viral quasispecies in the HBV RT region during pregnancy and postpartum abnormal alanine aminotransferase (ALT).

Method: Twenty-one chronic HBV infection pregnant women were included in this study. They received tenofovir disoproxil fumarate (TDF) or telbivudine (LdT) since the 28 ± 4th week of gestation for blocking MTCT of HBV and discontinued the therapy at delivery. Blood samples were taken at the baseline, 4 weeks of antiviral treatment, and 4–8 weeks after delivery. The next generation sequencing technique combined with bioinformatic methods were used to study the characteristics of quasispecies in the HBV RT region, and the dynamic changes of viral quasispecies heterogeneity during the treatment of and after the discontinuation of antiviral therapy were compared.

Results: During the treatment and after the discontinuation of antiviral drugs in pregnant women with chronic HBV infection, no significant changes were noticed in the quasispecies complexity and diversity of HBV RT region. The main effect between the time points, the main effect between the two groups did not reach statistical significance ($p > 0.05$) in the value of the shannon entropy (Sn) or the Hamming distance. Resistance associated variants (RAVs) (Frequency ≥0.1%) could be detected in all patients in both the TDF group and LdT group. Apart from a patient in the TDF group who had a mutation frequency of 1.32% in A181 T at 4 weeks postpartum (this value was 0.79% before treatment), all RAVs were detected at low frequency (<1.0%). The quasispecies complexity of HBV RT during pregnancy in the postpartum ALT abnormal group was significantly higher than that of the postpartum ALT normal group. Baseline quasispecies complexity (Sn) of HBV RT could predict the postpartum ALT abnormality, and the area under the ROC curve was 0.897 (95% CI, 0.749~1.000, $p = 0.007$).

Conclusion: 1. Short duration treatment of antiviral therapy during pregnancy had no significant effect on quasispecies heterogeneity in HBV RT region, with low potential risk of drug-resistant mutations. 2. The baseline (28 ± 4 week of gestation) HBV RT quasispecies complexity could predict the postpartum ALT abnormality in pregnant woman with chronic HBV infection.

Viral hepatitis A/E: Clinical aspects

SAT399

Significant compartment-specific impact of the RNA extraction and quantification method on the sensitivity of hepatitis E virus detection: implications for clinical care?

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Background and Aims: The hepatitis E virus (HEV) is the most common cause of acute viral hepatitis worldwide and may lead to chronic infection in immunocompromised hosts. RNA detection in plasma/stool is the gold-standard for diagnosis and required to determine efficacy of antiviral treatment. The impact of different viral extraction and quantification methods on reported HEV RNA results is poorly investigated.

Method: We evaluated the performance of the RealStar HEV2.0 kit (Altona Diagnostics, RS) utilizing three different RNA extraction methods (MagNA Pure 96 DNA and Viral NA SV Kit, MgP; QIAamp Viral RNA mini Kit Qiagen; VRK; COBAS Ampliprep TNAi, TNAi). The WHO standard (plasma) and patient samples (stool) were used to determine the lower limit of detection (LLOD). The best performing extraction method was evaluated in a total of 307 longitudinally samples (stool and plasma) of patients with acute (n = 18) or chronic (n = 36) HEV infection and compared to results with the former diagnostic standard of our center (TNAi/FastTrack Diagnostic Kit FTD-67.1; FTD).

Results: In plasma, the LLOD was 49, 95 and 329 IU/ml for extraction with MgP, VRK and TNAi, respectively. The sensitivity in stool samples were best with extraction by TNAi (LLOD 21IU/ml) followed by the VRK (LLOD 528 IU/ml), and lowest with MgP. In longitudinal plasma samples (n = 252) of HEV infected patients, the combination of MgP/RS had a good agreement with TNAi/FTD ($r^2 = 0.82$). Due to better sensitivity in low viremic patients, MgP/RS could reveal 54 (35.1%) HEV RNA positive samples in all samples tested negative with TNAi/FTD (n = 145). In stool, utilization of TNAi/RS showed an r^2 of 0.82 compared to TNAi/FTD. Of all HEV negative samples tested with TNAi/FTD (n = 36), 15 (41.6%) were positive when analysed with TNAi/RS. In our cohort, plasma samples at end of ribavirin treatment (EOT) could be re-analysed with TNAi/RS in 26 chronically infected individuals. Strikingly, out of 13 patients who had a viral relapse after treatment, 2 patients were HEV RNA positive at EOT when tested with our former diagnostic standard (TNAi/FTD), while re-testing with MgP/RS revealed HEV RNA in 8 of 13. In patients with sustained virological response, all except of one patient with low viremia (21IU/ml, MgP/RS) were HEV RNA negative at EOT.

Conclusion: Different methods for RNA extraction and quantification have a significant, compartment-specific impact on the sensitivity of HEV detection. Knowledge about the favourable combinations of extraction and quantification has important implications in particular for the identification of patients at risk for viral relapse after treatment.

SAT400

Effectiveness of hepatitis A vaccination in human immunodeficiency virus-infected men who have sex with men during an outbreak of hepatitis A in Osaka, Japan

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Background and Aims: The number of notified cases of hepatitis A among men who have sex with men (MSM) has rapidly increased in Japan since 2018. In our recent paper, sequence analysis has shown that hepatitis A virus (HAV) isolated from patients' serum or stool samples were identical to the EuroPride strain (RIVM-HAV16-090), one of the major HAV strains identified from the European outbreaks since 2016, suggesting that the current outbreak HAV strain was imported from Europe via sexual contact among MSM. The hepatitis A outbreak among MSM is still ongoing in Japan. In order to control this outbreak among MSM and to prevent further outbreaks spreading into the general population, we are encouraging MSM patients to receive vaccination for hepatitis A. In this study, we examined the effectiveness of hepatitis A vaccination in HIV-infected MSM.

Method: This is a retrospective study at our hospital in Osaka, Japan. A total of 212 HAV-seronegative and human immunodeficiency virus (HIV)-positive MSM patients who received hepatitis A vaccination between January 2011 and June 2019 were included. Patients received three doses of HAV vaccine (Aimmugen, Kaketsuken, Japan; the only licensed inactivated hepatitis A vaccine in Japan) at week 0, 4, and 24. Anti-HAV IgG antibody was determined between week 28 and 36. Predictive factors for HAV seroconversion were assessed by univariate and multivariate logistic regression analysis.

Results: The baseline characteristics of all patients at initial vaccination were as follows (continuous variables are expressed as median): age, 44 years old; sex (male/female), 212/0 and CD4 lymphocyte count, 497/μL. All patients received antiretroviral therapy and viral suppression (HIV-RNA <50 copies/mL) was maintained in 195 patients. Anti-HAV IgG antibody titers after vaccination ranged from 0.17 to 16.10 signal-to-cutoff ratios, and HAV seroconversion occurred in 203 patients (95.8%). Both univariate and multivariate analysis showed that high initial CD4 lymphocyte count (odds ratio = 5.38, 95% confidence interval [1.37–21.1], P = 0.016) was found to be statistically significant predictive factors for HAV seroconversion.

Conclusion: This study indicated that three doses of Aimmugen achieved good immune response against HAV in HIV-infected MSM patients and that high initial CD4 lymphocyte count can be a predictive factor for HAV seroconversion.

SAT401

Histopathology of hepatitis E is associated with patients' immune status and preexisting liver condition

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Background and Aims: Infection with the hepatitis E virus (HEV), a leading cause of acute hepatitis, represents a significant global disease burden. Given that, hepatitis E histopathology is hitherto relatively poorly characterized, and it is unknown what causes its remarkable variability. Thus, we aimed at a systematic analysis of hepatitis E histology and its association with clinical parameters.
Method: Fifty-two liver tissue samples (48 biopsies and 4 resection specimens) from 41 patients with molecularly proven hepatitis E (27 HEV genotype (gt) 3, three gt 1, one gt 4 and 10 undetermined gt infections) were systematically analysed for 33 histopathologic features. Findings were subjected to hierarchical clustering and resulting clusters analysed for their association with clinical parameters.
Results: Twenty-three of the 41 (56%) patients were immunocompromised, whereas 18 (44%) had no evidence of immunosuppression. Five patients (12%) had preexisting liver disease (LD). The histopathologic spectrum ranged from nearly normal over acute, chronic, and steatohepatitis to subtotal necrosis patterns of injury. Hierarchical clustering identified three main histopathologic clusters (C1-C3) which segregated along the patients' immune status and preexisting LD: C1 comprised mostly patients with preexisting LD; histology mainly reflecting the preexisting LD did not point to hepatitis E. C2 comprised mainly immunocompromised patients; histology displayed little active inflammation. C3 comprised almost all immunocompetent patients; histology displayed more active inflammation. Accordingly, the three clusters differed markedly with respect to their clinical and histopathologic differential diagnoses.
Conclusion: Hierarchical clustering unraveled three main groups of hepatitis E with distinct histopathologies, suggesting that these reflect biologically different manifestations of the disease. The association of histopathologic changes with the patient's immune status and preexisting liver condition might explain the diversity of hepatitis E histopathology and suggests that these factors are the key underlying determinants. Our results may help to improve patient management by guiding the clinico-pathological diagnosis of hepatitis E.

SAT402
Epidemiology of fulminant hepatitis A cases in Vienna - an informative case series

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Background and Aims: Hepatitis A virus (HAV) may lead to severe hepatitis with a fulminant course. Recent reports suggest a rising incidence of severe HAV cases in certain risk groups.
Method: We retrospectively identified patients with HAV-IgM (+) serology and/or confirmed viremia (HAV-RNA+) between Q1/2008 and Q3/2018. We defined severe HAV cases as an ALT/AST elevation >5×ULN and fulminant HAV cases as HAV patients with ALT/AST>5×ULN presenting with one of the following: (i)hepatic encephalopathy (HE) or ammonia levels>100 μmol/L, (ii)coagulopathy with INR>1.5 or (iii)jaundice with bilirubin >5 mg/dL.
Results: 579 HAV-IgM/RNA (+) patients were identified (44% male, age: 60 [IQR: 33] years) including 62 (11%) with HAV-RNA (+). HAV genotype was available in 25 patients (1A: 16; 1B: 6; 3A: 3). 69 (11.9%) patients showed severe HAV infection – including 39 (6.7%) patients with a fulminant HAV course. Sexual transmission was suspected in 3 (4%) in MSM patients with severe/fulminant HAV.
Most common symptoms of severe acute HAV infection were nausea/vomiting (63%), fatigue/malaise (52%), abdominalgia (47%), fever (43%), jaundice (39%), dark urine (30%), diarrhea (20%), hepatomegaly (19%). 37 (53.6%) patients with severe HAV were hospitalized, and 6 (9%) required ICU support. The number of HAV-IgM (+)/year was 101.5, 59, and 20.7 for the periods before 2010, 2010–2015, and 2015–08/2018, while the proportion of fulminant HAV cases increased from 6% and 3% to 21%, respectively.
Peak transaminases were higher in fulminant (AST: 1523 ± 2243.5, ALT: 2806 ± 2330 IU/mL) than in severe cases (AST: 468 [1396.5] $p < 0.001$, ALT: 535 [1617.5] IU/mL, $p < 0.001$).
In severe/fulminant HAV cases, the peak of bilirubin levels and INR occurred after a median of 3 [5] and 0 [1] days after peak ALT, respectively.
Patients with severe/fulminant HAV were younger (33 vs. 61 years) and more often male (50.7% vs. 43%), as compared to non-severe HAV cases. Genotypes in fulminant cases were: (1A: 12; 1B: 2). One patient (2.6%) with fulminant HAV required LTX. In severe/fulminant cases 30-day mortality after HAV diagnosis was 1/69 (1.6%).

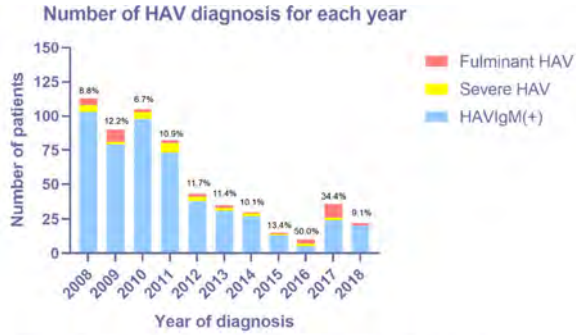

Fig.1- Yearly incidence of HAV IgM/RNA (+) with non-severe, severe and fulminant disease course, with yearly percentages of severe/fulminant disease course

Conclusion: In recent years, we observed a relative increase in the rate of fulminant HAV cases at the General Hospital in Vienna. Unvaccinated MSM might represent an emerging risk group for HAV infection. One fulminant HAV case required LTX. 30-day mortality after HAV diagnosis in severe/fulminant disease course was 1.6%.

SAT403
Epidemiology of fulminant hepatitis E cases in Vienna - an informative case series

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Background and Aims: While the role of hepatitis E virus (HEV) infection in immunocompromised and organ transplant recipients is recognized, it is also important to increase knowledge on clinical symptomatic cases in immune competent patients.

Method: The electronic records of the Vienna General Hospital were systematically screened for HEV-IgM (+) and/or HEV-RNA (+) results detected between Q1/2008-Q3/2018. Severe HEV cases were defined as ALT >5×ULN, while a fulminant course of HEV was defined as ALT>5×ULN plus one of the following criteria: (i) encephalopathy or ammonia levels >100 μmol/L, (ii) coagulopathy with INR>1.5 or (iii) jaundice with bilirubin>5 mg/dL.

Results: We identified 216 patients with HEV infection, of which 67 (31.9%) and 25 (11,6%) patients showed a severe and fulminant course, respectively. Previous travels to high-HEV endemic countries were recorded in 16 (23.9%) severe and in 10 (45.5%) fulminant cases. HEV-RNA was tested in 149/216 (69.0%) patients; but only, 19/149 (12.8%) were PCR+.

While the median age was 45 [IQR:31] in acute HEV it was 45 [IQR:31] and 36 [IQR:27.25] years in severe and fulminant HEV. The most common symptoms of severe/fulminant HEV were abdominalgia 70.2%, Icterus 32.9%, fever 26.9%, dark urine 23.9%, fatigue 23.9%, 20.1%.

Patients with severe/fulminant HEV were hospitalized in 32/67 (49.2%) cases and admitted to intensive care in 2/67 (3.0%) cases.

The incidence rates of HEV in the periods Q1/2008–2010, 2011–2015, and 2015-Q3/2018 were 21, 39.5, and 0.5, while the annual incidence of severe/fulminant courses of HEV was 3.5, 11.5, and 3.5, respectively. Peak levels of ALT (2347.5 [1975.25] vs. 307.5 [400.1] IU/mL, p < 0,001) and bilirubin (10.7 [7.9] vs. 1.08 [1.038], p < 0.001) were higher in fulminant HAV than in severe HAV cases. In fulminant HEV cases, peak bilirubin and INR occurred in a median 1 [2] day and 1 [10] days, respectively, after peak ALT.

Compared to all non-severe acute HEV cases, patients with severe/fulminant HEV were younger (48.5 vs. 23 years), more often male (54.6% vs 58.2%; p = 0.013). Patients with fulminant HEV more often had ascites (22.7% vs. 2.4%) and hepatic encephalopathy (18.2% vs. 2.4%). Liver transplantation was scheduled in 4 (5.9%) of severe/fulminant HEV cases but was ultimately never required. The overall 30-day mortality after diagnosis of severe /fulminant HEV was n = 1 (3.4%).

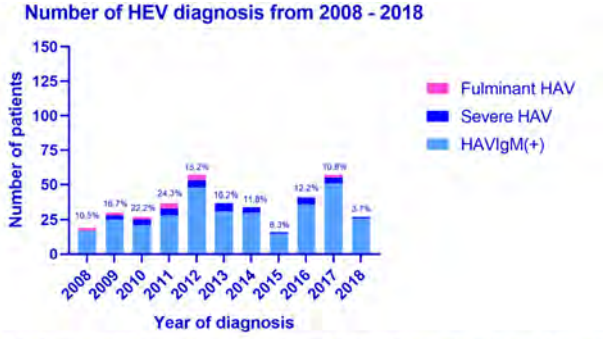

Fig.1 - Number of HEV diagosis per year form Q1/2008 to 3Q/2018, percentage of severe/fulminant disease courses for each year are given above the corresponding bar

Conclusion: Over the last 10 years we observed a stable annual rate of patients presenting with acute HEV at the Vienna General Hospital. Patients with severe and fulminant courses of HEV infection had most often recent travels to high HEV endemic countries. Cases with a chronic course of HEV infections remain to be identified.

SAT404

Impact of acute kidney injury in patients with acute hepatitis A

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Background and Aims: Patients with acute hepatitis A (hep-A) are at risk of developing acute kidney injury (AKI) due to intolerance to oral intake. Few small studies have suggested worse outcomes of patients with hep-A and AKI. We aimed to investigate the impact of AKI on hospital related outcomes in these patients through a large database analysis.

Method: We queried the National Inpatient Sample (NIS) from 2004 to 2014 to identify the hep-A related hospitalizations with coexisting AKI through ICD-9CM codes. Primary outcomes included prevalence of AKI in patients with hep-A with secondary outcomes as in-hospital mortality, length of stay (LOS) and inflation adjusted total hospitalization charges and cost. We used univariate and multivariate regression analysis to adjust for confounding factors to predict for mortality and increased resource utilization.

Results: We recorded a total of 10,005 of hep-A hospitalizations with 502 (5.02%) having AKI between 2004–2014. Patients in AKI group were older, mean age 61 vs 45 years old, 41% were females and 54.20% had government insurance. A total of 150 patients died within the hospital and 74 (49.34%) had AKI. Mean LOS (6.8 vs. 4.10 days), mean total hospitalization charges (62,436$ vs.27,073$) and mean total hospitalization cost (17,216$ vs. 8,326$) were recorded in AKI group. AKI was found to be an independent predictor of mortality (adjOR: 13.56, p < 0.01) after adjusting for confounders.

Table: Demographics and outcomes related to acute hepatitis A hospitalizations with and without AKI

	Acute Hep A with AKI *n* or *(%)*	Acute Hep A without AKI *n* or *(%)*	*p* value
No. of patients	502 (5.02%)	9503 (94.8%)	
Patient Characteristics			
Female	206 (41%)	4919 (51.76%)	<0.001
Age in years (Mean)	60.37	56.64	<0.001
Race			P = 0.43
White	68.84	56.74	
Black	5.15	8.36	
Hispanic	18.38	22.65	
Other			
Hospital Characteristics:			
Hospital Teaching Status			P = 0.95
Teaching	2.52	48.44	
Non-Teaching	2.46	46.58	
Hospital size			P = 0.63
Small	9.97	11.97	
Medium	22.53	25.36	
Large	67.5	62.68	
Hospital Location			<0.001
Rural	1.16	9.79	
Urban	112.59	76.46	
Hospital Region			P = 0.65
Northeast	28.38	27.42	
Midwest	17.29	19.74	
South	30.48	33.68	
West	23.85	19.16	
Primary and Secondary Outcomes			
Mortality	74	150	
Length of Stay (days)	6.8	4.1	
Total Hospitalization Charges (USD)	62,436$	27,073$	
Total Hospitalization Cost (USD)	17,216$	8,326$	

Conclusion: Our study shows that AKI leads to worse outcomes in hospitalized patients with acute hep-A. However, it is preventable with replenishing fluid loss in an effective manner in these patients.

SAT405

Are we aligned with WHO international strategy to eliminate hepatitis C by 2030: real-world data from Khyber Pakhtunkhwa, Pakistan

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Background and Aims: Pakistan has the second highest prevalence and burdens of hepatitis C virus (HCV) in the world. According to a meta-analysis, it is believed to chronically infect approximately 6.2% of the Pakistani population. Most of these cases are as a result of syringe reuse and unscreened blood product transfusions. G3-HCV represents 79% of all HCV infections in Pakistan. It is vitally important to treat the current epidemic unfolding in Pakistan in a cost-effective way. This study aimed to investigate the epidemiology of HCV genotypes in sixteen large districts of KPK. We also look at the recurrence rate and factors associated with poor response to DAAs which could impact WHO goal to eradicate HCV from the world by 2030.
Method: We looked at the HCV database held at Peshawar Medical College Teaching Hospital between January 2017 to April 2019. The HCV transmission via possible routs was evaluated by detailed questionnaire.
Results: Total of 1547 cases of active ECV infection were identified. The most prevalent genotype of HCV was recorded 3a (61.73%), followed by un typable (18.62%), 1a (16.16%), mixed genotypes (2.52%), 1b (0.71%), 3b (0.19%) and 2a (0.06%). Majority of the HCV patients in the KPK population acquire HCV due to the uses of unsafe injections (60.70%). Genotype 3a and 1a were seen more frequently in patients with past history of dental or medical surgery and blood-transfusion, respectively. Total 39 mixed genotypes patients were observed. In these 39 patients' genotypes 3a-1a were found in 32 individuals (82.05%) whereas the 3a-2a genotype was observed in 3 patients (7.69%), 4a-3a 2 patients (5.13%), 3a-1b in 1 patient (2.56%) and 2a-1a in 1 patient (2.56%). All eligible patients were treated with Sofosbuvir based regimens and overall SVR of 92% was achieved. Poor response rate was observed in mixed and un typeable genotypes. Relapse/reinfections were due to unsafe use of injectable needles.
Conclusion: Current study identified the major risk factor of HCV as the unsafe medical practices which transmit the HCV in the KPK population. Intravenous injections, unsafe dental and medical surgeries and visits to unhygienic barbers' shops were the main culprit. Mixed and un typeable genotypes were regarded as the major group with inadequate SVR. We are not aligned with WHO international strategy in Pakistan at present and therefore urgently need to focus our attention on the health care professional's awareness and public especially in rural areas to avoid the uses of unsafe injections/needles to control the further transmission of HCV infections.

SAT406

Hepatitis E seroprevalence and rate of viremia in immunocompromised patients - a systematic review and meta-analysis

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Background and Aims: Immunocompromised patients are at higher risk for acquisition of hepatitis E virus (HEV) infections. Chronification of hepatitis E may lead to life-threatening liver cirrhosis. However, prevalence of HEV infections in different cohorts of immunocompromised individuals remains conflicting. Aim of the study was to estimate the anti-HEV seroprevalence and the rate of HEV-RNA positivity among transplant recipients and patients with HIV infection.
Method: For this systematic review and meta-analysis we performed a literature search (PubMed) from 1996–2019 assessing studies reporting anti-HEV seroprevalence and HEV-RNA positivity. Data were stratified by assay, patient cohort (nature of transplantation, HIV-1) and methodological quality (according to JBI). Studies reporting on patients with elevated liver enzymes were analyzed separately. Datasets were pooled and analyzed using a linear mixed-effects meta regression model, which estimated seroprevalence rates based on pooled studies.
Results: 119 studies reporting the anti-HEV IgG seroprevalence and 78 studies reporting rate of HEV-RNA positivity were included in the final analysis. In 14.629 transplant recipients seroprevalence (range: 6%–29%) did not differ significantly compared to 23.692 HIV-1 positive patients (range: 4%–19%), p = n.s. HEV-RNA positivity was significantly higher in transplant recipients than in patients with HIV (1.16% vs. 0.4%; $p < 0.05$; Fig. 1). Subgroup analysis showed highest rates of HEV-RNA positivity in lung transplant recipients (2.1%) and lowest in liver transplant recipients (0.9%). Focusing on immunosuppressed individuals with elevated liver enzymes rates of HEV-RNA were significantly higher in transplant recipients compared to HIV positive patients (2.1% vs. 0.4%; OR 5.2, $p < 0.05$).

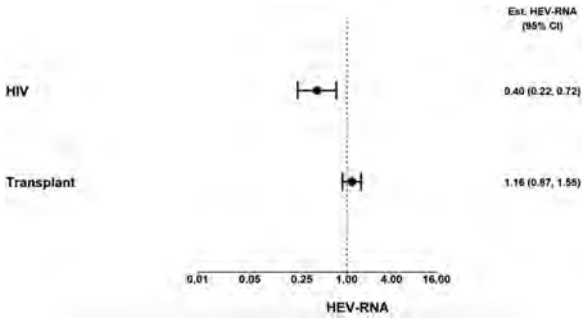

Figure 1: HEV-RNA positivity in two patient cohorts (HIV, Transplant) with normal liver values in percent ($p < 0.05$).

Conclusion: HEV infections are common among immunocompromised individuals. Interestingly, rates of HEV-RNA positivity, indicating ongoing infection, were significantly higher in transplant recipients compared to those with HIV-1. In a subgroup with elevated liver enzymes HEV-RNA detection was 5 times higher in transplant recipients compared to HIV patients. These findings support the assumption that transplant patients are at higher risk of chronic HEV infection than HIV patients at comparable exposure rates.

SAT407

Therapeutic window for ribavirin therapy in transplant recipients with chronic hepatitis E virus infection

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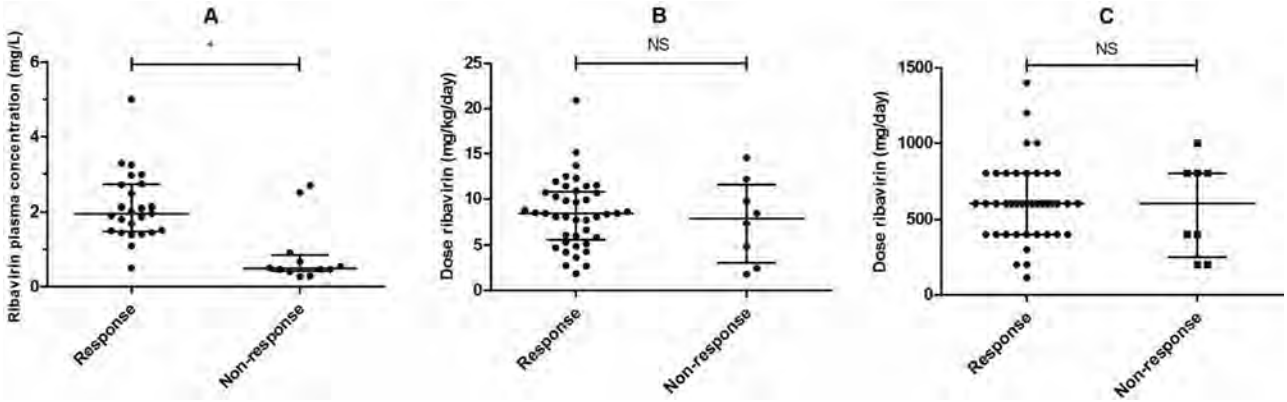

Figure: (abstract: SAT407): Ribavirin steady-state plasma concentration and dose versus response and non-response in patients with a chronic HEV infection.

Background and Aims: The optimal dose, target concentration and duration of ribavirin (RBV) therapy in solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients with chronic hepatitis E virus (HEV) infection are unknown. The aim of this study was to investigate the association between RBV plasma concentrations and virologic response and anemia. Consequently, define the therapeutic window for RBV in SOT and HSCT recipients with a chronic HEV infection.
Method: In this retrospective, multicenter, cohort study, data of adult SOT and HSCT recipients with chronic HEV infection, who had been treated with RBV monotherapy between 2008 and 2018 were included. Data were collected in four European university hospitals. A sustained virologic response (SVR) was defined as an undetectable level of HEV RNA in serum at least 6 months after completion of RBV therapy. A clinically relevant response to RBV was defined as a decrease of the HEV RNA load after the initiation of RBV therapy with at least a factor 2. No response was defined as a rise in the HEV load. Receiver operating characteristic curve analyses were performed and the half-maximal effective concentration was calculated to determine a representative therapeutic window. Factors associated with a SVR were investigated using multiple binary logistic regression analysis.
Results: A total of 96 patients with 300 RBV plasma determinations (RBV concentration range 0.10–7.40 mg/L) were included. RBV monotherapy for a median of three months resulted in a SVR in 62.5% of the patients and 88.5% of the patients developed anemia. RBV plasma concentrations at steady-state were significantly higher in the response group compared to the non-response group: median 1.96 (IQR 1.81–2.70) versus 0.49 (IQR 0.45–0.73) mg/L, p = 0.0004. RBV caused dose-dependent hemoglobin reduction with higher RBV plasma concentrations resulting in more hemoglobin reduction.
Conclusion: RBV monotherapy resulted in a SVR in 62.5% of the patients. RBV plasma concentrations at steady-state were significantly higher in the group with a virologic response. The therapeutic window for RBV for treating a chronic HEV infection in SOT and HSCT recipients ranges between 1.8 and 3.0 mg/L.

SAT408

Does glucose-6-phosphate dehydrogenase deficiency affects morbidity in acute viral hepatitis? A case control study from a tertiary care hospital in Karachi, Pakistan

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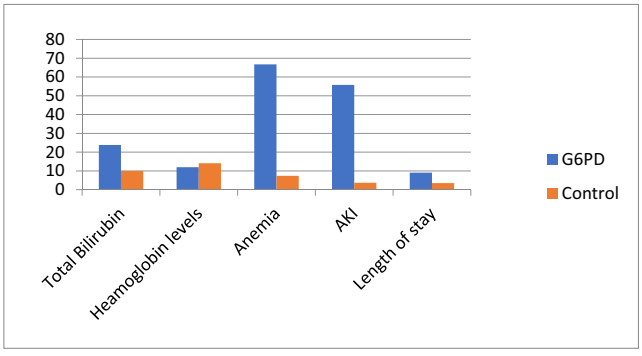
Background and Aims: Viral hepatitis is known to be one of the significant causes of morbidity and mortality globally. In patients with glucose 6 phosphate dehydrogenase deficiency (G6PD), acute viral hepatitis may be associated with complications such as severe anemia, hemolysis, renal failure, hepatic encephalopathy and even death. In this study we will compare the parameters of morbidity and outcomes in patients of acute hepatitis with and without co-existing G6PD deficiency.
Method: Nine male patients with acute viral hepatitis and diagnosed G6PD deficiency were compared with 27 matched control patients presented with acute viral hepatitis, from January 2012 to December 2018.
Results: The patients with G6PD deficiency had a significantly raised mean total bilirubin levels as compared to controls (23.8 ± 17.4 vs 10.0 ± 8.8 mg/dl, respectively, p < 0.01), Direct and indirect bilirubin levels were also significantly raised in patients with G6PD deficiency. Mean Hemoglobin levels were low in G6PD patients in comparison to the control group (12.0 ± 2.6 vs 14.07 ± 2.6 g/dl, respectively, p = 0.05). Hemolysis was seen in 22.2% of G6PD group. Anemia was more prevalent in G6PD patients as compared to controls (66.7% vs 7.4%, respectively, p < 0.02). Acute kidney injury in G6PD group was significantly high as compared to control group (55.8% vs 3.7%, respectively, p < 0.02). Only one patient in each group required hemodialysis. The most common etiology was hepatitis A in both group (66.7% vs 44.4%) followed by hepatitis E. The average duration of stay was prolonged in G6PD patients (9.1 ± 12.2 vs 3.5 ± 1.5 days, respectively, p < 0.05). No significant difference was seen in symptoms, prothrombin time, liver enzymes and outcome in both groups i.e. recovery was seen in both groups.



Conclusion: Acute viral hepatitis in patients with G6PD has a more severe clinical course due to complications leading to prolonged hospital stay but no difference was seen on overall clinical outcome of patients.

SAT409

Hepatitis E virus genotype 3 subtype dependent clinical outcomes in Belgium 2010–2018

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Background and Aims: Except for immunosuppression, male gender, age >50 and chronic liver disease, no correlators with clinical outcomes of a Hepatitis E Virus (HEV) genotype (gt) 3 infection have been identified. In Belgium, diagnosis of HEV is centralized at the National Reference Center (NRC) for Viral Hepatitis, Sciensano. We analyzed virological factors and clinical outcomes in a nationwide cohort of HEV patients.

Method: Demographic, clinical and biochemical parameters of HEV infections documented at the NRC were collected between 2010–2018. Serum HEV –IgM, –IgG and HEV RNA were determined by ELISA and RT qPCR. HEV was subtyped by Sanger sequencing of an ORF2 fragment. Odds ratios (OR), risk ratios (RR) and 95% confidence intervals (95% CI) were calculated using STATA.

Results: 402 cases were identified. Among 300 cases with clinical data, the median age was 57 years and 69% were males. HEV viremia was detected in 211 patients with an available genotype in 177. HEV gt3 infections largely predominate (93% [165/177]) with subtypes 3c (38% [67/177]) and 3f (44% [78/177]) almost equally represented. The percent of immunocompromised patients (30% vs 16%; OR3c = 2.2 [1.0–4.7] p = 0.045) was higher for patients infected with a virus from the clade of gt3c (achi), compared to a virus from the clade of gt3f (efg), while a similar but non-significant trend was observed for pre-existing liver cirrhosis (9.9% vs 3.4%; OR3c = 3.1 [0.8–12.5]). Patients with a HEV gt3f infection had higher peak values of ALT (mean of 2199 vs 1528 U/L; p = 0.005) and bilirubin (mean of 8.6 vs 4.1 mg/dl; p = 0.001) compared to a HEV gt3c infection. In addition, HEV gt3c infections were treated more in ambulatory settings, while the percent of patients admitted to the hospital was higher for HEV gt3f cases (36% for 3c; 61% for 3f; RR3f = 1.7 [1.2–2.4] p = 0.003). There were no differences between the subtypes in intensive care unit admissions (5.7%), in hospitalization durations (median of 4.0 weeks), in chronicity (18% vs 14%, RR3f = 0.8 [0.4–2.0]) nor in deaths (1.4% vs 4.8%; RR3f = 3.4 [0.4–30]).

Conclusion: A similar number of HEV gt3c and gt3f infections have been diagnosed in Belgium. Despite more pre-existing comorbidity in patients infected with HEV gt3c, HEV gt3f infections are associated with a more severe disease course according to laboratory values and hospitalization rates. Our nationwide analysis is the first to identify a correlation between HEV gt3 subtype and clinical outcomes.

SAT410

Hepatitis E virus infection in liver transplant recipients in Sweden

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Background and Aims: Liver-transplanted patients with acute hepatitis E virus (HEV) infection are at risk developing a chronic infection, which may rapidly progress to severe liver damage if not treated. However, the prevalence of HEV infection after liver transplantation remains largely unclear and likely varies geographically. Thus the aim of this study was to investigate the prevalence of acute and chronic HEV infection among liver transplant recipients in an HEV endemic region.

Method: During 2013–2018, 116 liver-transplant recipients were prospectively enrolled. They were evaluated for anti-HEV IgM and IgG antibodies as well as HEV RNA at the time of liver transplantation, and 6 and 12 months post transplantation. Additionally, medical records were reviewed.

Results: Seven (6%) had detectable HEV RNA, of whom six acquired their infection post-transplantation and one had detectable HEV RNA prior to transplantation. Additionally, 4 (3%) patients had serological markers indicative of HEV infection without detectable HEV RNA. Signs and symptoms of HEV infection were subtle, none were diagnosed in routine clinical care, and none developed a chronic HEV infection. Furthermore 15 patients (13%) had reactive anti-HEV IgG serologies in pre-transplant samples.

Conclusion: A substantial proportion of liver transplant recipients in Sweden are at risk of acquiring acute HEV infection, but surprisingly, no chronic HEV infection were detected in the present study. As HEV infections are often discrete and not diagnosed by current clinical practise, and as ribavirin therapy is available, the introduction of routine prospective HEV RNA screening of liver transplant recipients may be warranted.

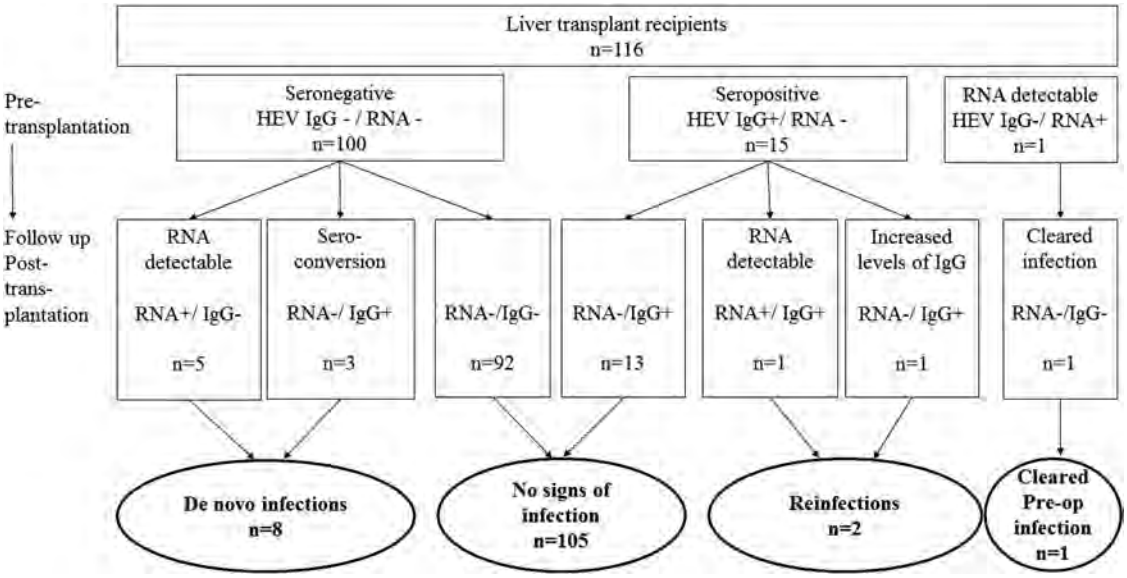

Figure: (abstract: SAT410)

SAT411

Hepatitis E virus shedding in semen of chronically, but not acute HEV infected individuals

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Background and Aims: Various viruses have been reported to be present in semen and possibly outlast the duration of viremia indicating replication beyond the blood-testis barrier. Acute and chronic hepatitis E virus (HEV) genotype 3 infections have been associated with extrahepatic manifestations, but replication in the testis has never been documented. Thus, we studied presence of HEV in semen of patients with acute or chronic HEV infection.

Method: Three chronically HEV infected (2 heart transplant recipients, 1 lymphoma patient) and 5 immunocompetent patients with acute HEV infection were included in the study – in all patients semen, urine, stool and blood were screened for HEV PCR positivity. In addition, HEV presence in testis, was analyzed in 12 experimentally HEV-infected (genotype 3) male pigs (using dilutions of the inoculum from 10^{-4} to 10^{-8}, corresponding to a dosage of up to 14.746 IU/dose) by PCR. The study has been approved by the local ethics board.

Results: 2/3 chronically HEV infected patients (one genotype 3i, two genotype 3c) tested positive for HEV in semen with concentrations 3–4 log higher than viral load in serum. Under treatment with ribavirin HEV viremia disappeared in both patients. In one of them high HEV level in semen outlasted the duration of viremia for >12 weeks (see Figure 1), while viral load in semen in the second patient strongly decreased but remained positive for 20 weeks longer than viremia. In contrast none of 5 semen samples from immunocompetent patients with acute, self-limited HEV infection (viremia range from 24 to 160.442 IU/ml) tested positive for HEV. Furthermore, in none of the 12 experimentally HEV infected immunocompetent pigs HEV could be found in the testes, while 8/12 tested positive for HEV in their livers, 7/12 in various lymph node localisations, 6/12 in their gallbladders, 5/12 in their spleens and 8/12 in the feces.

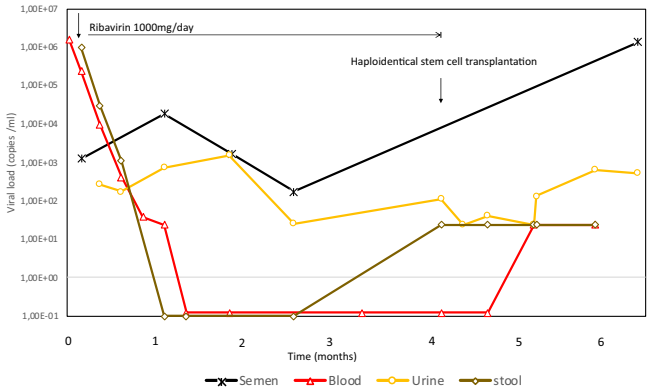

Figure: HEV viral load in semen, blood, urine and stool in a 66-year old patient with chronic hepatitis E under condition of a B-cell lymphoma, undergoing subsequent allogenic stem cell transplantation.

Conclusion: HEV can persist in semen of patients with chronic but not acute infection >5 months longer than viremia. These results imply the testes to be a niche of HEV replication without an adequate access of the immune system. Larger studies are warranted to elucidate whether chronic HEV infection could potentially be transmitted through sexual activity.

Viral hepatitis B/D: Therapy

SAT412

Pradefovir in naive or experienced adult patients with chronic infection of hepatitis B virus: week24 results from 23 multicentre, double-blind, randomised, non-inferiority, phase2 trials

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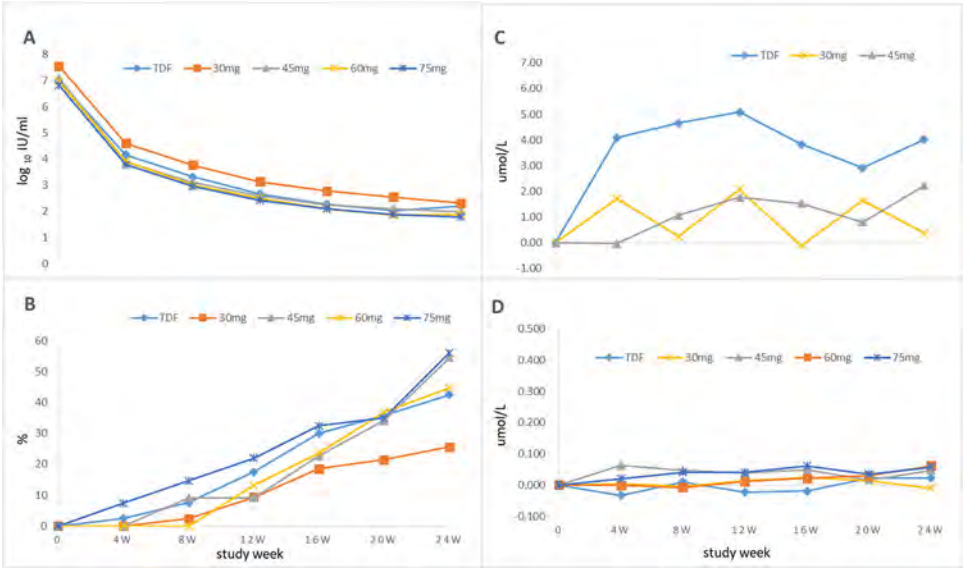
Background and Aims: Pradefovir is a liver-targeting oral prodrug of adefovir, a nucleotide analog with antiviral activity against HBV DNA polymerase. The phase 2 study is to evaluate the safety and tolerability of multiple oral doses of pradefovir 30 mg, 45 mg, 60 mg, and 75 mg, compared to tenofovir disoproxil fumarate (TDF) 300 mg.

Method: Treatment-naïve and experienced (not on treatment period greater than 6 months) patients including those with advanced fibrosis (F3) or compensated cirrhosis (F4) (≤10%). The primary objective was to evaluate the safety and tolerability of multiple oral doses of pradefovir 30, 45, 60, 75 mg, compared to TDF 300 mg once daily for 24 weeks and to identify the most appropriate dose of pradefovir for the forthcoming Phase 3 study.

Results: A total of 240 subjects were randomized and treated in the study. Approximately 48 patients in each group. All patients received >1 dose (ITT). Patient were 100% Chinese; 76% male with average age of 35.5 (±9.8) years. Around 80% were HBeAg positive and about 10% had liver cirrhosis. The demographics of each treatment groups were similar to the study population as a whole. Mean baseline HBV DNA was 7.24 (±1.33) log10 IU/ml. and mean baseline ALT was 156.5 (±79.3) U/L. The majority of patients had previously received antivirals or IFN. Reductions from baseline in HBV DNA at week 24 were 5.40, 5.34, 0.5.33, 5.40 log10 IU/ml for pradefovir 30, 45, 60, 75 mg respectively vs 5.12 log10 IU/ml for TDF group. The proportion of patients with HBV DNA <169 copies/ml were 27.1, 54.2, 47.9, and 58.3% for pradefovir 30, 45, 60, 75 mg group respectively and 41.7% for TDF group (Figure A and B). A dose response relationship was demonstrated for the pradefovir treatment group. The proportion of patients with HBeAg loss at 24 weeks were 2.86%, 12.12%, 6.45%, 9.09% for pradefovir 30, 45, 60, 75 mg group respectively and 3.03%% for TDF group. The more significant changes of serum creatinine in TDF group compared to pradefovir 30 or 45 mg groups from baseline to 24 weeks and serum phosphorous were comparable between all pradefovir groups and TDF (Figure C and D). Most frequently reported AEs included cholinesterase decreased (45%), creatine kinase MB increased (31%), Hypophosphatemia (8%). Most of AEs were mild (grade I). There were no treatment related SAEs were reported. Overall AEs and laboratory abnormality were comparable to TDF 300 mg group.

Conclusion: The reductions in HBV DNA with pradefovir treatment groups demonstrated comparable/or superior to the control TDF once daily group. A higher rate of HBeAg loss in receiving pradefovir treatment groups were observed comparing to the TDF 300 mg treatment group.



SAT413

Combination of NA, PEG-IFN alpha-2b and GM-CSF enhanced hbsab production in NA experienced CHB patients (the anchor a study): an interim analysis

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Background and Aims: Granulocyte-macrophage colony stimulating factor (GMCSF) has various effects on immune responses and has previously been used as an adjuvant to HBV vaccine to enhance the antibody response. This multicenter, randomized controlled trial (NCT02327416) was to evaluate whether combination of NA, peginterferon alfa-2b (Peg-IFN α-2b) and GMCSF could induce HBsAg loss/seroconversion in patients undergoing long-term NA.

Method: 249 CHB patients who had received NA>1 year, with HBsAg <3000 IU/ml and HBV DNA ⩽1000 copies/ml, were randomized 1:1:1 to receive ETV for 96 weeks (Group I) or ETV for 48 weeks and Peg-IFN a-2b (180 μg/week) for 96 weeks (Group II) or ETV and intermittent GMCSF (75 μg/day, first 5 days each month) for 48 weeks plus Peg-IFNα-2b for 96 weeks (Group III). Interim data on 249 patients (81 in Group I, 83 in Group II and 85 in Group III) were analyzed.

Results: Baseline characteristics were comparable among treatment groups. At week 96, patients receiving triple combination therapy (NA+ Peg-IFN+ GMCSF) and patients receiving dual combination therapy (NA+ Peg-IFN) achieved higher rates of HBsAg loss than those continuing NA treatment (19.40%, 31.34% and 0%, respectively, $p < 0.001$ for all comparisons vs Group I). There was no significant difference in HBsAg loss rate between Group III and Group II ($p = 0.527$). Rates of HBsAb ≥ 10IU/ml were significantly higher in Group III (32.76%) and Group II (34.43%) than Group I (0%, $p < 0.001$ for all comparisons vs Group I). HBsAg seroconversion was only observed in Group III (20.69%) and Group II (27.87%) ($p = 0.3619$). At week 12 after initiating Peg-IFN, 58 patients in Group III and 47 in Group II had normal or mild elevated ALT levels (<2 × ULN), among these subgroup of patients, triple combination therapy induced significantly higher HBsAb positivity rates than dual combination therapy (48.28% vs 29.79%) at week 96. The difference between the two groups and the 95% CI was 18.49% (0.15% to 36.83%), which was statistically significant. Moreover, numerically higher rates of HBsAb>100IU/L were observed in Group III than in Group II at week 96 (17.24% vs 8.51%, $p = 0.19$). Both dual and triple combination therapy regimens were generally well-tolerated.

Conclusion: For patients with virological suppression by NA, a combination of ETV and Peg-IFN α-2b therapy with or without GMCSF significantly increases rates of HBsAg loss/seroconversion. GMCSF may enhance the therapeutic effect of Peg-IFN α-2b in terms of HBsAb positivity in those with normal or mild elevated on-treatment ALT levels.

SAT414

Efficacy and safety of treatment interruption in patients with HBeAg negative chronic hepatitis B

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Background and Aims: in patients with HBeAg negative chronic hepatitis B (CHB), HBsAg loss rarely occurs during nucleos(t)ids analogues (NUC) therapy (<1% yearly). Recent studies show that NUC discontinuation may increase HBsAg loss rates and in the EASL Guidelines it is suggested that this therapeutic strategy can be considered. The aims of this study were to determine the rates of HBsAg loss after NUC discontinuation and its predictive factors. As a secondary aim we evaluated the safety of this therapeutic strategy.

Method: prospective open study of non-cirrhotic patients with CHB HBeAg negative, with at least 3 years of NUC therapy. HBsAg levels (IU/ml), DNA (IU/ml), anti-HBs and transaminases were determined at weeks 0, 4, 12, 24, 36, 48 and subsequently, every 6 months. HBcrAg (log/ml) was determined at week 0. Retreatment criteria were defined as acute hepatits (ALT >10 UNL confirmed at 2 weeks or ALT 5–10 UNL confirmed at 4 weeks) and persistent hepatitis as ALT 2–5 UNL and DNA >2000 IU/ml for at least 6 months.

Results: from From December 2017 to October 2019, NUC was interrupted in 57 patients. The median (range) age was 52 (29–80) years, 74% were male. The pre-treatment time with NUC was 8.5 (3.2–17.3) years; tenofovir in 37 (64.9%), entecavir in 17 (29.8%), lamivudine in 2 (3.5%) and telbivudine in 1 (1.7%). Baseline HBcrAg levels were 2.5 (<2.0–4.1) and HBsAg levels of 687 (0.2–14637). After a median follow-up of 51 (4–99) weeks, 5 (8.8%) patients lost the HBsAg: one patient at week 4, two at week 24 and two at week 36. Patients who lost HBsAg showed a longer treatment duration (median: 14 years) and lower values of HBsAg (19.8) than patients who did not eliminate HBsAg, 8 years ($p = 0.002$) and 827 IU/mL ($p = 0.003$) respectively. HBsAg loss was achieved in 5 (15.2%) of 33 patients with HBsAg <1000 ($p < 0.046$). All patients who lost HBsAg ($n = 5$) had received a minimum of 9 years of NUC ($n = 24$) ($p = 0.006$). There were no differences between groups in terms of age, gender, ethnicity, type of NUC or HBcrAg levels. During the follow-up, only 2 (3.5%) patients have required to restart the NUC due to acute hepatitis, with excellent response to treatment while 96.5% of patients remain without retreatment criteria.

Conclusion: Treatment discontinuation in patients with chronic hepatitis B HBeAg negative increases the rate of HBsAg loss and is a safe strategy. All the patients that lost HBsAg had levels <1000 IU/ml and had a minimum of 9 years of treatment prior to the interruption. After one year of follow-up, 96.5% of patients remain without antiviral treatment.

SAT415

Pegylated interferon beta strongly reduces all serological and intrahepatic hepatitis B virus parameters in immunodeficient humanized mice

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Background and Aims: Pegylated interferon-alpha (peg-IFN-alpha) remains a valuable finite therapy for chronic hepatitis B (CHB) infection because it provides higher rates of HBsAg seroclearance compared to treatment with polymerase inhibitors. Peg-IFN-beta, which is used in multiple sclerosis treatment, acts on the same cellular receptor. While IFN-alpha promotes cccDNA epigenetic suppression and destabilisation, knowledge of IFN-beta antiviral activity towards HBV is limited. Aim of this study was to investigate the efficacy of peg-IFN-beta, in comparison to peg-IFN-alpha, to lower viremia, levels of circulating viral antigens and intrahepatic viral loads in vivo, in a system lacking adaptive immune response.
Method: Human liver chimeric uPA/SCID/IL-R2γ (USG) mice stably infected with HBV (GT-D) received either peg-IFN-beta or peg-IFN-alpha (Plegridy® or Pegasys® 25 ng/gr, twice/week) for 6 weeks while a group of infected mice remained untreated. Serological and intrahepatic virological changes were determined by qRT-PCR, ELISA and IHC. HBx protein was determined by WB and ChIP-qPCR was performed to assess SMC6 interaction with the cccDNA.
Results: Expression of human interferon stimulated genes (ISGs) strongly and similarly increased in both treated groups (e.g. peg-IFN-beta: ISG15 = +2.6Log, MXA = +2.4Log, OAS = +1.8Log), compared to the untreated controls. Compared to baseline, median HBV DNA viremia declined 2.6Log and 1.2Log after peg-IFN-beta and peg-IFN-alpha treatment, respectively. Notably, median reduction of circulating HBsAg levels appeared stronger upon peg-IFN-beta administration (−1.1Log), compared to peg-IFN-alpha (−0.4Log). Median HBeAg reduction was 1.5Log and 0.54Log in mice receiving peg-IFN-beta or peg-IFN-alpha, respectively. Intrahepatically, peg-IFN-beta appeared superior to peg-IFN-alpha in reducing total HBV DNA/cell (−1.4Log vs −1Log), total HBV RNA (−1.1Log vs −0.5Log) and pgRNA (−1.6Log vs −0.6Log). HBcAg staining was markedly reduced in both treated groups, while SMC6 staining reappeared in nuclei of human hepatocytes. Moreover, IFN treatment reduced HBx in both groups and SMC6 was found associated to the cccDNA, despite overall cccDNA reduction.
Conclusion: Administration of peg-IFN-beta promoted more profound direct antiviral effects in vivo than peg-IFN-alpha in immunodeficient humanized mice, leading to a strong decline of all viral markers, including HBx and SMC6-associated epigenetic silencing of the persisting cccDNA.

SAT416

hzVSF, a novel HBV therapeutic candidate, shows WHsAg loss in woodchuck hepatitis model and safety in phase I clinical study

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Background and Aims: hzVSF, humanized immunoglobulin G4 targeting membrane-bound vimentin of virus0infected cells, exhibited anti-replicative and anti-inflammatory effect in HBV-infected human hepatocytes. The purpose of the current studies was to evaluate antiviral effect of hzVSF in acute and chronic woodchuck hepatitis virus (WHV)-infection models. Furthermore, we examined the safety of the hzVSF and pharmacokinetics (PK) profile in healthy volunteers.
Method: 1) To evaluate the efficacy of hzVSF in acute WHV-infected woodchucks, we examined the viral titer, serum transaminases, bilirubin, and liver hepatopathology after hzVSF treatment. 2) In chronic WHV infection model, the efficacy of hzVSF monotherapy and combination therapy with tenofovir alafenamide fumarate (TAF) was assessed. 3) Phase I clinical study of intravenous (iv) single ascending dose of hzVSF up to 1200 mg was conducted to elucidate the safety and pharmacokinetics in healthy volunteers.
Results: 1) In acute WHV woodchuck model, hzVSF treatment attenuated clinical symptoms of acute infection, including body weight loss, the elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin level, and immune cell infiltration into the liver tissue. 2) In chronic woodchuck model, monotherapy of hzVSF showed the suppression of WHV DNA and WHsAg in 25% of animals, no rebound was observed after cessation of hzVSF treatment. Fifty percent of WHV-infected animals in the combination treatment group (hzVSF+TAF) showed the reduction of WHV DNA and WHsAg to baseline (LLOQ) and no relapse after the cessation of treatment. 3) In phase I study, single iv dose of hzVSF showed tolerability and safety with no serious adverse effects up to top dose and dose-proportional PK profile.
Conclusion: hzVSF exhibits anti-viral and anti-inflammatory effects in WHV-infection models and safety in phase I study. This potential novel HBV treatment warrant further clinical studies in chronic HBV infection patients.

SAT417

Safety and efficacy of up to 76 weeks 10 mg (high dose) bulevirtide monotherapy in compensated cirrhotics with delta hepatitis

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Background and Aims: Administration of entry inhibitor Bulevirtide (BLV) 10 mg/day + TDF has been shown to be effective and safe in HDV hepatitis. However, its effectiveness and safety beyond 48 weeks and the kinetics of virological and clinical relapse after discontinuation have never been demonstrated in a real-life setting.
Method: Three patients with compensated HDV cirrhosis and contraindication to Peg-IFN were treated with BLV 10 mg/day + TDF for up to 76 weeks (Case 1: 69 years, female, HDV RNA 23,600 IU/mL, ALT 140 U/L; Case 2: 51 years, male, concomitant autoimmune hepatitis, HDV RNA 392,000 IU/mL, ALT 232 U/L; Case 3: 58 years, female, autoimmune thrombocytopenia, HDV RNA 5,900,000 cp/mL, ALT 244 U/L). Liver function tests, total bile acids, and HBV/HDV markers were monitored. HDV RNA was quantified by RoboGene (LOD <6 IU/mL) or by in-house RT PCR (LOD <100 cp/mL).
Results: In Case 1, HDV RNA became undetectable by week 36 and ALT normalized by week 20, both markers remained negative up to week 52 when BLV was withdrawn. After BLV discontinuation, HDV RNA became detectable after 2 weeks (24 IU/mL), progressively increased up to week 16 (13,655 IU/mL) and then declined to 431 IU/mL at week 38 post-treatment. A similar pattern was observed for ALT levels that progressively increased >ULN from week 14 to week 30 (41→333 U/L), and then declined, without any signs of lab/clinical decompensation. At last available sample, 38 weeks after BLV

discontinuation: HDV RNA 431 IU/mL, ALT 70 U/L. HBsAg progressively declined from 22 IU/mL at EOT to 0.20 IU/mL at last sampling. In Case 2 and Case 3, BLV treatment was continued for 76 weeks. Both patients achieved and maintained a biochemical and virological response through week 76 with no evidence of virologic breakthrough or biochemical elevations. At week 76, HDV RNA was <6 IU/mL and 150 cp/mL, and ALT 33 and 35 U/L, respectively while no significant changes of HBsAg were observed during treatment. In Case 2, a significant improvement in portal hypertension features and liver function tests were documented, as well as a reduction of plasma cell infiltration and histological activity in the liver biopsy performed at week 72.
BLV was well tolerated in all 3 patients, without any clinical drug-related adverse events except for an asymptomatic increase in bile acids.
Conclusion: Up to 76 weeks of Bulevirtide 10 mg/day monotherapy is safe and effective in patients with HDV related compensated cirrhosis.

SAT418

Correlation between HBV core-related antigen and the new quantitative IGG anti-core in treated caucasian HBeAg-negative patients and inactive carriers with and without a functional cure

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Background and Aims: Hepatitis B core-related antigen (HBcrAg) and the quantitative assessment of IgG antibodies against HBV core antigen (qAnti-HBc IgG) are new HBV biomarkers that however have not been compared. The study aimed to assess their relationship in HBsAg positive and negative patients, with and without oral therapy.
Method: This cross-sectional/longitudinal retrospective study evaluated 411 sera from 4 groups of Caucasian patients: Group 1: 189 HBsAg-positive, HBeAg-negative patients under long-term TDF/ETV; Group 2: 28 patients who cleared HBsAg during NUC therapy; Group 3: 87 inactive carriers; Group 4: 22 inactive carriers who cleared HBsAg. qAnti-HBc IgG (Fujirebio) were quantified as cut-off index (COI), and HBcrAg levels (Fujirebio) were expressed as LogU/mL (LLD<2.5 Log U/mL, quantification range 3.0–7.0).
Results: In 189 Group 1 patients [age 66, 47% cirrhosis CPT A, 95% gt D, 65% NUC-experienced, TDF/ETV treated for 100 months, undetectable HBV DNA for 118 months, HBsAg 517 (1–11,781) IU/mL], median qAnti-HBc IgG was 127 (6–282) COI, while HBcrAg 3.0 (2.5–5.3; 56% <LLD) LogU/mL. At multivariate analysis, low qAnti-HBc IgG were associated only with longer HBV DNA suppression (OR 1.02, $p < 0.001$) while low HBcrAg only with lower qHBsAg. All the 105 HBcrAg negative patients tested positive for qAntiHBc IgG [123 (2–282) COI]. In samples collected after one year, qAnti-HBc declined from 107 to 85 COI, qHBsAg from 250 to 202 IU/mL, while HBcrAg remained stable (2.8 vs 3.0 LogU/mL; 50%<LLD).
The 28 Group 2 patients who cleared HBsAg during NUC [age 59, 36% cirrhosis CPT A] were divided into two subgroups, according to NUC indication (CHB vs recent HBV infection): qAnti-HBc was lower in the former than in the second subgroup [58 (14–222) vs 209 (59–285) COI ($p = 0.010$)] and HBcrAg 3.0 (2.5–4.1) vs 3.2 (2.6–4.5) LogU/mL, but 59% vs 18% <LLD ($p = 0.033$), respectively.
In Group 3 [age 53, qHBsAg 321 (0.12–52,000) IU/mL], qAnti-HBc were 267 (75–299) COI and HBcrAg 2.7 (2.5–3.9; 76%<LLD); patients with <267 COI had lower qHBsAg and HBV DNA, however only the latter significant (OR 1.00, $p = 0.028$). In Group 4 (age 64, 27% with anti-HBs) qAnti-HBc were 226 (138–277) COI and HBcrAg 2.8 (95% <LLD). Overall, patients under NUC have both lower qAnti-HBc and HBcrAg level ($p < 0.0001$).
Conclusion: Anti-HBc IgG and HBcrAg levels are reduced by NUC treatment but have different kinetics, thus representing additional useful markers for the management of HBV patients.

SAT419

The establishment of hepatitis B care and treatment clinics with viral load testing capacity in the United Republic of Tanzania: a demonstration project following WHO guidelines, Zanzibar, 2017–2019

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Background and Aims: In 2015 about 257 million persons were living with chronic hepatitis B worldwide and about 887,000 related deaths occurred. Zanzibar is a low-resource semi-autonomous nation with a hepatitis B prevalence of about 2%. To mitigate this burden, in 2015 the World Health Organization (WHO) issued hepatitis B care and treatment guidelines. We report early results of the implementation of hepatitis B care and treatment programs in Zanzibar.
Method: A five-year demonstration project was launched December 2016 at Mnazi Mmoja Hospital in Zanzibar. Clinical and laboratory staff at each site received training on the delivery of hepatitis B-directed care and laboratory testing. Participants were recruited from Zanzibar's National Blood Donation Program where donors are systematically screened for HIV, hepatitis C antibody (anti-HCV), syphilis, and hepatitis B surface antigen (HBsAg). Participants were invited to participate in the program if they tested negative for HIV and anti-HCV, and were HBsAg-positive. Participants were examined for clinical signs of liver disease and received hepatitis B-related laboratory testing every 6–12 months for assessment of treatment eligibility. Specimens were sent to a lab in Dar es Salaam for hepatitis B virus (HBV) DNA testing. Tenofovir disoproxil fumarate (TDF) was provided for participants meeting WHO guidelines eligibility. Clinical and laboratory data were collected for programmatic evaluation purposes.
Results: After 34 months, 587 participants enrolled: 360 with complete laboratory results, 154 with two clinic visits, and 70 with ≥3 clinic visits. Of those with complete lab results, the median age was 34 years (IQR 28–41), 218 (61%) male. Of these, 26 patients were started on TDF: 17 who met the criteria for liver cirrhosis, and/or 15 with APRI >1.5, 3 met WHO criteria by HBV DNA and ALT; 1 discontinued due to intolerance from fatigue. ALT values decreased among those treated, from a median of 98.5 (IQR 44–246) to 34.5 (IQR 25–62) ($p = 0.06$). Of enrolled patients, 1 was diagnosed with hepatocellular carcinoma and 5 patients died due to complications from HBV-associated liver disease. Challenges included patients presenting with advanced liver disease.
Conclusion: Hepatitis B care and treatment is feasible in low-resource settings. While challenges remain, testing and linkage to care is critical to decrease the global burden of hepatitis B.

SAT420

Nucleos(t)ide analogue therapy decreases the HBeAg loss rate in HBeAg positive chronic hepatitis B patients with hepatitis flare: a propensity score matching study

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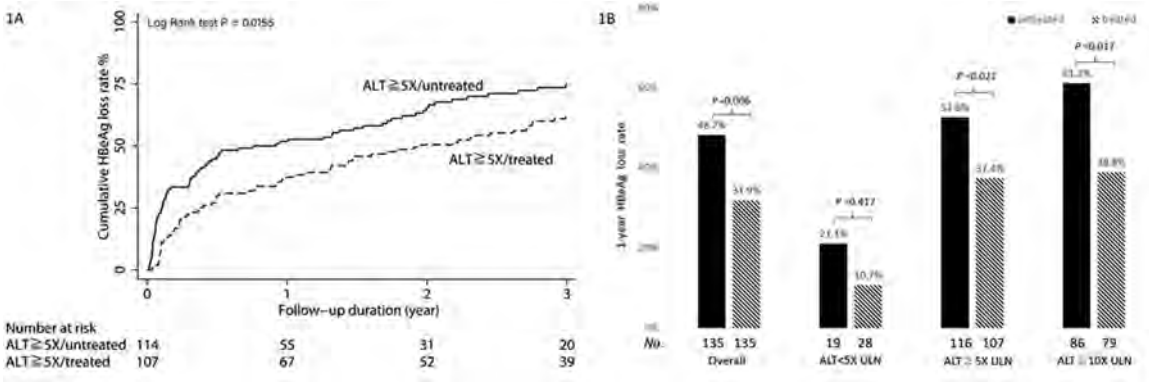

Figure: (abstract: SAT420): Kaplan-Meier curve of hepatitis flare patients with or without treatment after PSM; 1B:1-year HBeAg loss rate between treated and untreated HBeAg positive patients after PSM.

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Background and Aims: Asian pacific guidelines have recommended that HBeAg positive patients with hepatitis flare deserve 3 months close monitoring for spontaneous HBeAg loss if there is no concerns for hepatic decompensation (Liaw YF et al. Hepat Int 2012). In contrast to earlier findings during lamivudine therapy (56%/62 vs. 25%/28, Perrillo RP et al, Hepatology 2002), a recent study involving 51 patients showed lower HBeAg loss rate after immediate nucleos(t)ide analogue (Nuc) therapy (30% vs. 47%) than that of the untreated patients with ALT >10X upper ULN (Brahmania M et al CGH 2019). These controversial findings from 2 studies with small number of patients require larger studies to clarify.
Method: HBeAg positive CHB patients received Entecavir or Tenofovir monotherapy during 2006–2017 were recruited as treated cohort (Study group) while those without anti-viral treatment during 1980–2000 were enrolled as untreated cohort (Control group). Patients without proper monitor of ALT level, co-existence of other liver diseases and follow-up less than one year were excluded. Propensity score matching (PSM) was performed to adjust the difference between the Study and Control groups including age, gender, genotype, cirrhosis, ALT level and alfa-fetoprotein (AFP) level with 1:1 ratio. Logistic regression was performed to investigate predictors for 1-year HBeAg loss.
Results: A total of 270 patients were analyzed with 135 patients in each arm after PSM. No differences of age, gender, genotype, cirrhosis, ALT level and AFP level were noted between two groups. The overall one-year HBeAg loss rate was lower in the study than in the control group (31.9% vs. 48.2%, P = 0.006) especially when patients encountering hepatitis flare (ALT ≥ 5X ULN) (Figure). In multivariate analysis, ALT level ≥ 10X ULN (<5X as referent, adjusted OR: 5.44, P < 0.001) and Nuc treatment (untreated as referent, adjusted OR: 0.52 (0.31–0.88), P = 0.015) were independent predictors for HBeAg loss by 1 year.
Conclusion: Nuc therapy resulted in lower HBeAg loss rate. Endogenous host immune driving toward HBeAg loss may be halted by Nuc therapy especially in those with hepatitis flare. The results add support to the recommendation of Asian-Pacific guidelines.

SAT421

Long-term risk of primary liver cancers in tenofovir versus entecavir treatment for chronic hepatitis B

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Background and Aims: It remains controversial whether tenofovir disoproxil fumarate (TDF) and entecavir (ETV) treatment is associated with different clinical outcomes for chronic hepatitis B (CHB). We compared the long-term risk of TDF versus ETV on primary liver cancers including hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (CCC) in CHB patients from a large multi-institutional database in Taiwan.
Method: From 2011 to 2018, a total of 21,222 CHB patients who had received TDF or ETV in seven medical institutes constituting the Chang Gung Memorial Hospitals were screened for eligibility. Patients with coinfection, preexisting cancer, missing data and less than 6 months of follow-up were excluded. Finally, 7,248 patients (5,348 and 1,900 in the TDF and ETV groups, respectively) were linked to the National Cancer Registry database for the development of HCC or CCC. Propensity score matching (PSM) (1:2) analysis was used to adjust for baseline differences.

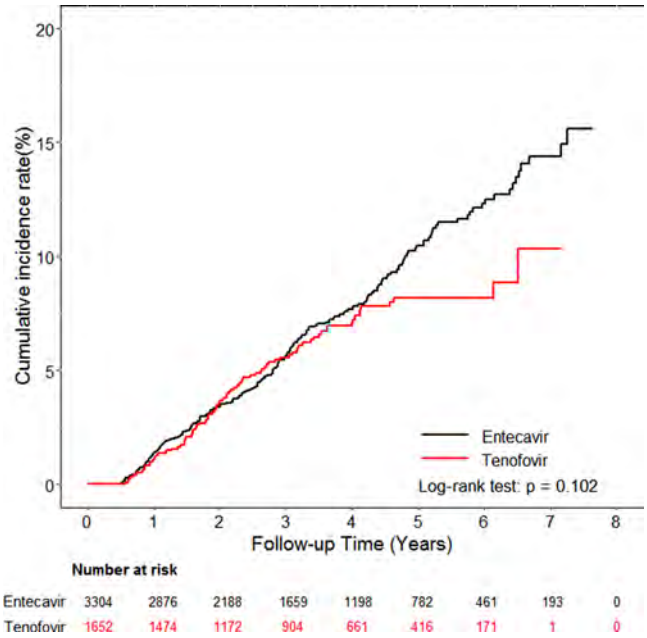

Figure: Cumulative incidence of HCC in PSM population.

Results: The incidence rate of HCC was not different in the entire population (hazard ratio [HR] 0.89; 95% confidence interval [CI] 0.71 to 1.12, p = 0.315) and in the PSM population (HR 0.87; 95% CI 0.69 to

1.11, p = 0.274) after adjusting baseline factors. In the subgroup analysis, TDF treatment was associated with a lower risk of HCC than ETV treatment (HR 0.54; 95% CI 0.30 to 0.98, p = 0.043, PSM model) among decompensated cirrhotic patients. There was no difference between TDF and ETV groups in the incidence rate of CCC (HR 1.84; 95% CI 0.54 to 6.29, p = 0.330 in the entire population and HR 1.04; 95% CI 0.31 to 3.52, p = 0.954 in the PSM population, respectively).

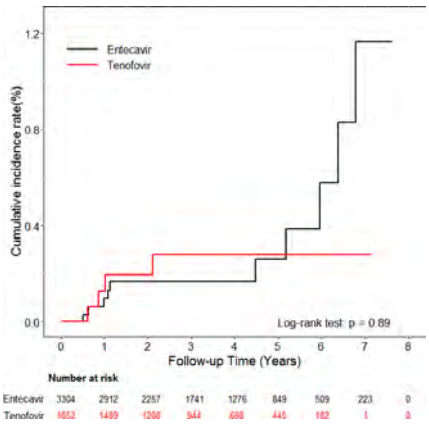

Figure: Cumulative incidence of CCC in PSM population.

Conclusion: Treatment with TDF and ETV showed a comparable long-term risk of HCC and CCC in CHB patients, whereas TDF appeared to be a lower risk of HCC than ETV in decompensated cirrhotic patients.

SAT422

ATI-2173, a novel phosphoramidate nucleoside prodrug for HBV cure regimens

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Background and Aims: ATI-2173 is a liver-targeted phosphoramidate prodrug of clevudine (CLV) designed to deliver the 5′-monophosphate of CLV to the liver, decreasing systemic exposure to CLV and potentially enhancing anti-HBV activity. Unlike chain terminating nucleos(t)ide analogues, the active 5′-triphosphate of ATI-2173/CLV has unique antiviral properties as a non-competitive, non-chain terminating HBV polymerase inhibitor. CLV produced extended post-exposure reductions of HBV DNA in the woodchuck HBV model and in man but clinical development was stopped when reversible proximal skeletal myopathy was observed with exposures of >8 months (median 18 mo.).
Methods: *In vitro* studies are ongoing in primary human hepatocytes and liver cell lines. Hepatic extraction was measured in portal/jugular vein cannulated cynomolgus monkeys dosed IV and orally.
Results: ATI-2173 has an anti-HBV EC_{50} of 1.71 µM with a CC_{50} >100 µM in HepG2.2.15 cells. The EC_{50} dropped 1000-fold to 1.31 nM in primary human hepatocytes without evidence of cytotoxicity. ATI-2173 has low serum protein binding with low fold-change in EC_{50} *in vitro* in the presence of increasing concentrations of human serum. *In vitro* combination studies of ATI-2173 activity against HBV in primary human hepatocytes demonstrated additive antiviral activity with TDF, lamivudine, and GLS4 (CAM inhibitor); and synergistic activity with entecavir (ETV), adefovir and interferon. *In vitro* drug resistance studies confirm mutational cross resistance with lamivudine, telbivudine, and ETV but not HBV capsid inhibitors or TDF. ATI-2173 had no *in vitro* genotoxicity and a negative hERG assay. ATI-2173 liver-targeting was confirmed in the rat and cynomolgus monkey with an 82% hepatic extraction ratio after an oral dose in the monkey.
Conclusions: ATI-2173 is a potent liver-targeted molecule that delivers the 5′-monophosphate of clevudine, enhancing the anti-HBV activity while significantly reducing systemic exposure to clevudine in the rat and monkey. ATI-2173 combined with TDF, ETV or other direct acting antivirals, could become an integral part of combination HBV cure regimens.

SAT424

Impact of ESC+ technology on the hepatic safety profile of GalNAc-delivered, HBV-targeting RNAi therapeutics

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Background and Aims: Ribonucleic acid interference (RNAi) therapies are a promising option for functional cure of chronic hepatitis B virus (HBV) infection and must have an acceptable safety profile in a patient population with underlying liver disease. Enhanced Stabilization Chemistry Plus (ESC+) RNAi design retains enhanced metabolic stability needed for in vivo potency while reducing sequence matched off-target effects. This improved specificity is hypothesized to result in better liver safety – the target organ of GalNAc-RNAi. To test the ability of ESC+ technology to improve hepatic safety profile in the clinic, we evaluated ALN-HBV and VIR-2218, two investigational HBV RNAi therapeutics designed to target all HBV transcripts. VIR-2218 was derived from ALN-HBV using ESC+ technology.
Method: RNA-Seq analysis was used to evaluate differential gene expression in human liver cells transfected with ALN-HBV or VIR-2218. Relative hepatotoxicity was assessed in a humanized mouse model in which the liver is populated with human hepatocytes. In separate clinical studies, normal healthy volunteer cohorts (randomized 3:1 active:placebo) received single subcutaneous doses of 0.1, 0.3, 1 and 3 mg/kg of ALN-HBV (Study ALN-HBV-001) or 50, 100, 200, 400, 600 or 900 mg of VIR-2218 (Study VIR-2218–1001).
Results: RNA-Seq analysis in human liver cells showed reduced off-target effects with VIR-2218 compared with ALN-HBV, as expected with ESC+ design. In addition, human ALT1 levels were notably lower in a humanized liver mouse model with VIR-2218 compared to ALN-HBV, consistent with the improved specificity of VIR-2218. In humans, transient ALT elevations were observed with ALN-HBV in 1/6 (17%) and 4/6 (67%) subjects after a single dose of 1 and 3 mg/kg, respectively. These elevations were asymptomatic and not accompanied by hyperbilirubinemia. In contrast, no ALT elevations potentially related to VIR-2218 were observed with single doses of VIR-2218 ranging from 50 to 600 mg (~0.8 to 10 mg/kg). At 900 mg (~15 mg/kg), mild ALT changes have been observed in a subset of subjects.
Conclusion: ESC+ design appears to improve the hepatic safety profile of HBV-targeting RNAi, an important consideration in this patient population, especially in those with advanced liver disease. Evaluation of VIR-2218 in chronic HBV patients is ongoing.

SAT425

A once-per-week or every-two-week dosing regimen is more efficacious for the TIR7 agonist JNJ-64794964 (JNJ-4964) to induce an anti-hepatitis B virus (HBV) effect and HBV-specific immune responses in AAV-HBV mice

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Background and Aims: JNJ-64794964 (JNJ-4964/ AL-034/ TQ-A3334), is a novel, selective, oral Toll-like receptor 7 (TLR7) agonist currently in phase 1 clinical development for chronic hepatitis B (CHB) treatment. The aim of the present study was to investigate the effects of dosage and dosing frequency on the efficacy and safety of JNJ-4964 in an adeno-associated virus vector expressing HBV (AAV-HBV) mouse model.
Method: C57BL/6 mice infected with rAAV8-1.3HBV (genotype D) were treated orally with JNJ-4964 at doses ranging from 2 to 20 mg/kg and dosing frequencies of twice-per-week (BIW), once-per-week (QW), once-every-2-weeks (Q2W) or once-per-month (Q4W) (n = 8–10/group). After 12 weeks of dosing, mice were followed up for 4 weeks. The anti-HBV activity of JNJ-4964 was assessed on plasma HBV viral load, HBV surface-antigen (HBsAg) expression and anti-HBs antibodies, and liver HBsAg and HBV core antigen expression (HBcAg). The capacity of JNJ-4964 to induce plasma cytokine production and splenic HBV-specific immune responses were evaluated by ELISA and T- and B-cell ELISpot assays.
Results: Anti-HBV activity of JNJ-4964 increased in a dose-dependent manner, from 6 mg/kg onwards. At the same dose, declines in plasma HBV viral load, plasma HBsAg, liver HBsAg and HBcAg expression were more pronounced with higher dosing frequency. Plasma HBsAg levels became undetectable with the following regimens: from 6 mg/kg and above BIW, from 14 mg/kg and above QW, at 18 mg/kg Q2W. CXCL10, IFN-alpha, IL-12p40 and IFN-gamma were upregulated at all frequencies tested in a dose-dependent manner, however peak levels tended to decrease and not completely return to baseline upon repeated dosing with the BIW and QW dosing frequencies. QW dosing appeared more effective versus the other dosing frequencies tested for the induction of adaptive immune responses, e.g., increase in plasma anti-HBs antibodies and the induction of spleen anti-HBs IgG-producing B cells and of spleen HBs-specific IFN-gamma-producing T cells. No clinical signs or relevant changes in body weight gain were observed throughout the study.
Conclusion: JNJ-4964 dosing frequency impacted the extent of immune stimulation and anti-HBV effect that JNJ-4964 may trigger in AAV-HBV mice. To trigger adaptive immune responses, as well as an indirect anti-HBV effect, the QW dosing frequency was overall more efficient than the BIW, Q2W and Q4W dosing frequencies. Dosing frequency did not impact safety in AAV-HBV mice.

SAT426

In vitro and in vivo characterization of VIR-2218, an investigational RNAi therapeutic targeting hepatitis B virus

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Background and Aims: An RNAi therapeutic targeting HBV RNAs has the potential to contribute to functional cure with finite treatment by decreasing expression of viral antigens, including tolerogenic HBsAg. VIR-2218 is an investigational, N-acetylgalactosamine (GalNAc)-conjugated RNAi therapeutic created using Enhanced Stabilization Chemistry Plus (ESC+) chemistry that targets within the HBV X gene region shared by all HBV transcripts. VIR-2218 is currently in Phase 2 clinical development.
Method: In vitro activity and specificity of VIR-2218 were measured after transfection-mediated delivery of VIR-2218 in multiple cell-based systems. Pan-genotypic activity was determined using luciferase readout in a psiCHECK2-plasmid incorporating the HBx gene in Cos7 cells. HBV mRNA, HBsAg and HBeAg levels were measured in the HBV-expressing HepG2.2.15 cell line. The effects of VIR-2218 on HBsAg and HBeAg levels were also measured in HBV-infected HepG2-NTCP cells. In vivo, HBsAg levels were examined following single or multiple subcutaneous (SC) injections of VIR-2218 in mice transduced with AAV8-HBV encoding HBV genotype D.
Results: Evaluation of in vitro VIR-2218 activity at 50 nM in cells transfected with a psiCHECK2-HBV plasmid encoding sequences representing HBV genotypes A-J demonstrated X mRNA knock-down against all 10 genotypes (22.4% to 51.4% remaining). In HepG2.2.15 cells, VIR-2218 inhibited HBV mRNA in a dose-dependent manner, with an IC_{50} of 766 pM, 2.21 nM, and 499 pM for HBsAg mRNA, HBeAg and HBsAg, respectively. This potent inhibition was confirmed in an authentic infection model in HBV infected HepG2-NTCP cells. In the AAV-HBV mouse model, single SC doses of VIR–2218 at 0.3, 1, and 3 mg/kg resulted in sustained and dose-dependent– reduction of serum HBsAg (34%, 72%, and 92% maximum reduction, respectively). Additionally, mice receiving 1 and 3 mg/kg doses every other week × 6 or monthly × 3, or a single dose at 9 mg/kg, exhibited dose-responsive serum HBsAg reduction, with a maximum of 2.7- to 2.8–log reduction in the highest dose group.
Conclusion: VIR-2218 targets a highly conserved region of the HBV genome and demonstrates pan genotypic effects against HBV in vitro. In vivo, VIR-2218 demonstrates potent, sustained anti-viral activity in the AAV-HBV mouse model. These data support development of VIR-2218 for treatment of patients with HBV.

SAT427

Real-world experience from tenofovir alafenamide use in chronic hepatitis B: an Hellenic multicenter real-life clinical study (HERACLIS-TAF)

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Background and Aims: In the registrational trials 108/110, tenofovir alafenamide (TAF) compared to tenofovir disoproxil fumarate (TDF) was shown to have similar efficacy and improved safety in renal function and bone mineral density (BMD) parameters. However, those trials did not include chronic hepatitis B (CHB) patients with significant renal and/or bone disorders. In Greece, TAF has been reimbursed since February 2018 mostly for patients with impaired renal function [estimated glomerular filtration rate (eGFR) <60 ml/min or serum phosphate <2.5 mg/dl] and/or osteoporosis (T-score < −2.5). Thus, the aim of this study was to assess the characteristics of

CHB patients who started TAF based on the Greek reimbursement criteria and eventually the effectiveness and safety of TAF in such patients.

Method: Adult (≥18 years old) CHB patients who started TAF between 02/2018–10/2019 at 13 clinics participating in the HERACLIS-TAF registry were included. Main exclusion criteria were coinfection with hepatitis D virus, active malignancy and biphosphates use in the last 6 months. Demographic, clinical and laboratory characteristics as well as reason for TAF use were recorded. MDRD formula was used for eGFR estimation. PAGE-B score was calculated at TAF onset.

Results: In total, TAF therapy was initiated in 176 patients (71% males; age: 64 ± 12 years, 64% >60 years old): 11 (6%) nucleos(t)ide analogue (NA) naive and 165 (94%) NA experienced; 157/176 (89%) were directly switched to TAF from other NA(s) (138 from TDF) and 8 (5%) had discontinued NA(s) for >2 months (TDF: 6). The main reason for TAF use was renal in 96 (54%), BMD in 61 (35%) (osteoporosis 44, osteopenia 17) and both renal and BMD disorders/risks in 19 (11%) patients. At TAF onset, 56 (32%) and 24 (13.6%) patients had eGFR <50 and 50–59 ml/min and 19 (11%) patients had phosphate <2.5 mg/dL. Common comorbidities were: hypertension 50%, diabetes 24%, hemodialysis 6%, transplantation 4%. PAGE-B score was low (<10) in 13 (7.4%), moderate (10–17) in 67 (38%) and high (>17) in 60 (34%) patients.

Conclusion: CHB patients who receive TAF in Greece are different than those included in the registrational trials, as all patients have significant renal and/or bone disorders/risks and most patients are old (>60 years), NA(s) experienced with comorbidities usually have moderate/high HCC risk. Future research is expected to evaluate the effectiveness and safety of TAF in this real-world clinical setting.

SAT428

Early PEG-interferon-related ALT flares of high magnitude lead to HBsAg decline and loss. A study of 639 chronic hepatitis B patients

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Background and Aims: Serum alanine aminotransferase (ALT) flares play an important role in assessing nucleos(t)ide analogues (NA) discontinuation and during treatment with novel compounds aiming for functional cure (HBsAg loss). Flares can be a double-edged sword in chronic hepatitis B (CHB), as they may result in accelerated serological response but could also lead to liver failure.

Method: A post hoc analysis of four international randomized trials (HBV-99-01, PARC, ARES, PEGON) involving pegylated interferon (PEG-IFN-α-2a or α-2b)-based therapy was conducted to characterize ALT flares in CHB patients. Patients received PEG-IFN monotherapy (n = 260), de novo PEG-IFN+NA combination therapy (n = 128), PEG-IFN add-on to NA pretreatment (n = 123), or NA monotherapy (n = 128). A flare was defined as an episode of ALT elevation ≥5×ULN after start of therapy, with those occurring within the first 24 weeks considered 'early', and after 24 weeks, 'late'. Patients with NA withdrawal flares were excluded. Logistic regressions were performed to describe the association between flares and serum HBsAg levels.

Results: During a median follow-up of 72 weeks, 111/639(17%) patients experienced at least one flare. The median timing of the first flare was 12 weeks (IQR 4–60) and the median magnitude was 6.6xULN (IQR 5.5–8.6). The flare group was older (36 vs 33 yrs), mostly Caucasian (79% vs 55%), largely genotype A/D (40%/50% vs 22%/38%), with higher baseline ALT (3.5 vs 1.5×ULN), HBV DNA (7.8 vs 5.0 logIU/mL), and HBsAg levels (4.3 vs 3.9 logIU/mL), all p ≤0 .01. Almost all flares (99%) were found in patients who received PEG-IFN-based therapy. Flares were observed in 38/251(15%) patients with PEG-IFN added on NA vs 72/260(28%) with PEG-IFN monotherapy (p < 0.01). Among patients who received combination therapy, more flares were observed in the de novo PEG-IFN+NA therapy group compared to PEG-IFN add-on (36/128(28%) vs 2/123(2%), p < 0.01). In total, 131 patients achieved ≥1log decrease in HBsAg. In univariable analysis, early flare was significantly associated with ≥1 log decline in HBsAg (odds ratio (OR) (95% CI): 3.8 (2.3–6.2), p < 0.01), as were male sex and increasing magnitude and number of flares. In multivariable analysis, compared to having no flare, early flares were independently associated with ≥1log decline in HBsAg (OR: 4.0 (2.2–7.3), p < 0.01). Early ALT elevations ≥5×ULN had a significant effect on serum HBsAg decline (Figure; p < 0.01). Of the 22 patients who achieved HBsAg loss, 16(73%) had at least one flare, which all occurred early during treatment (p < 0.01). Neither decompensation nor death was observed with flares.

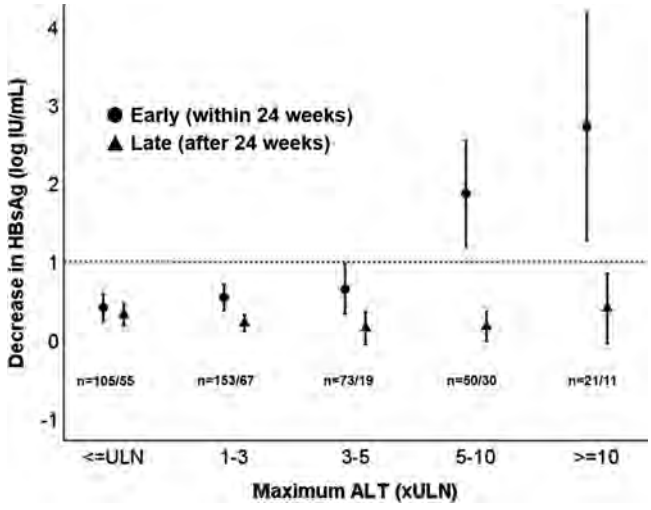

Figure: Association between of maximum serum ALT level and HBsAg decline, occurring early during treatment or late.

Conclusion: Early on-treatment flares were significantly associated with a greater decrease in serum HBsAg and with HBsAg loss compared to late flares or no flares.

SAT429

Safety and efficacy of switching to tenofovir alafenamide (TAF) in virally suppressed chronic hepatitis B (CHB) patients with renal impairment: week 48 results from a phase 2 open label study

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Background and Aims: Switching to TAF, a novel tenofovir prodrug, has shown maintenance of viral suppression with stable or improved bone and renal safety at Wk 24 in CHB patients with moderate to severe renal impairment (eGFR by Cockcroft-Gault [$eGFR_{CG}$] <60 mL/min) and ESRD patients on HD. We evaluated the safety and efficacy in these virally suppressed patients with renal impairment 1 year after switching to TAF in a Phase 2 study.

Method: CHB patients with renal impairment receiving TDF and/or other OAVs for ≥48 weeks and virally suppressed for ≥6 months with HBV DNA <20 IU/mL at screening were enrolled into 2 cohorts: 1) moderate-severe renal impairment (eGFRCG 15 to <60 mL/min) and 2) ESRD (eGFRCG <15 mL/min) on chronic HD. All patients were switched to TAF 25 mg QD for 96 weeks (given post-HD on days of dialysis for ESRD patients). Safety assessments including changes in bone (hip and spine BMD) and renal (CrCl by Cockcroft-Gault [$eGFR_{CG}$], serum creatinine) parameters, viral suppression, and biochemical responses were assessed in all patients at Week 48.

Results: 93 patients (mod-severe impairment 78; ESRD 15) were enrolled from 26 sites in 8 countries; 89% of patients remained on study at Week 48. At baseline, 74% were male, 77% Asian, 68% ≥60 y, 83% HBeAg-negative and median ALT was 17 U/L. Up to 25% overall (both cohorts) had osteoporosis at hip and/or spine, and a high proportion had comorbidities (60% HTN, 24% DM). Key efficacy/safety results at Week 48 are summarized in the Table. Efficacy (HBV DNA<20 IU/mL) was maintained in nearly all patients on treatment at Week 48 and a high proportion had normal ALT levels. Five patients discontinued study drug early (withdrew consent) with last available HBV DNA <20 U/mL; 1 patient had HBV DNA ≥20 IU/mL and 1 patient died. Relative to baseline levels, switching to TAF resulted in stable hip/spine BMD in moderate to severe renal impairment patients, with a slight decrease in hip BMD in ESRD patients. Slight improvements were observed in renal parameters including $eGFR_{CG}$ and markers of renal tubular function in moderate to severely impaired patients. TAF was well tolerated, with no Grade 3/4 or serious adverse events related to study drug.

Conclusion: In renally-impaired CHB patients, including ESRD patients on HD, viral suppression was well maintained, and the bone and renal safety were stable or improved 48 weeks after switching to TAF.

Table. Efficacy and safety results at Week 48

n/N (%) or median (Q1, Q3)	Moderate-Severe RI[a] n=78	ESRD on HD[b] n=15
Efficacy		
HBV DNA <20 IU/mL	72/78 (92)[c]	14/15 (93)[d]
ALT normal (2018 AASLD criteria)	68/78 (87)	12/15 (80)
ALT normalization (2018 AASLD criteria)	3/5 (60)	NA
HBsAg loss	0/78 (0)	1/15 (7)
HBeAg loss	0/13 (0)	0/3 (0)
qHBsAg, log_{10} change (IU/mL)	-0.04 (-0.10, 0.01)	-0.08 (-0.11, 0.01)
Bone parameters		
Hip BMD, % change	+0.27 (-0.67, 1.40)	-1.74 (-3.85, 1.17)
Spine BMD, % change	+1.06 (-0.83, 3.28)	-0.04 (-1.76, 3.63)
CTX, % change, (ng/mL)[e]	-20.5 (-38.5, 0.0)	-14.2 (-47.6, 11.4)
P1NP, % change, (ng/mL)[f]	-15.25 (-31.82, -0.76)	-20.55 (-35.62, 15.32)
Renal parameters		
Serum creatinine, change mg/dL	+0.03 (-0.07, 0.08)	NA
Serum phosphorus, change mg/dL	0.0 (-0.1, 0.4)	NA
$eGFR_{CG}$, change mL/min	+0.8 (-3.9, 2.4)	NA
RBP/Cr, % change, µg/g[g]	-42.4 (-67.4, -1.4)	NA
β2MG/Cr, % change, µg/g[h]	-50.9 (-81.1, 51.8)	NA

Efficacy results are missing equals failure (M=F)

[a]Moderate-severe renal impairment: $eGFR_{CG}$ 15 - <60 mL/min

[b]ESRD: $eGFR_{CG}$ < 15 mL/min on hemodialysis

[c]5 patients discontinued study drug early (withdrew consent) with last available HBV DNA <20 U/mL; 1 patient had HBV DNA ≥20 IU/mL

[d]1 patient died

[e]Serum C-type collagen sequence (bone resorption marker); [f]Serum procollagen type 1 N-terminal propeptide (bone formation marker)

[g]Urine retinol binding protein/creatinine (renal tubular marker); [h]Urine beta-2 microglobulin/creatinine (renal tubular marker).

Abbreviations: $eGFR_{CG}$, estimated creatinine clearance (Cockcroft-Gault method); ESRD, end-stage renal disease; BMD, bone mineral density by DXA scan); NA, not applicable

Figure: (abstract: SAT429)

SAT430

Residual low HDV viremia is associated with HDV RNA relapse after PEG-IFNa-based antiviral treatment of hepatitis D (delta): results from the HIDIT-II study

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Background and Aims: Treatment of hepatitis D virus (HDV) infection with pegylated interferon alfa (PEG-IFNa) is currently considered the standard of care (SOC). Previous studies demonstrated off-treatment HDV RNA responses in 25–31% of cases. Virological responses regarding HDV RNA were determined with in-house assays with rather high limits of detection. We here aimed to investigate the frequency and impact of low and very low HDV RNA viremia detectable with highly sensitive assays only (LV).
Method: We re-analyzed HDV RNA in samples collected in the HIDIT-2 trial (Wedemeyer et al., Lancet Infectious Diseases 2019) with the Robogene assay (RA; Jena Analytics). In the HIDIT-2 study, patients were treated with PEG-IFN-2a alone or in combination with tenofovir dipivoxil for 96 weeks. Complete samples were available for 93 patients at baseline, week 48, week 96 and follow-up week 24 (week 120). HDV RNA was extracted by manual extraction according to the package insert. The lower limit of detection (LOD) of Robogene assay is 14 IU/ml, quantitative results were here reported above 100 IU/ml only. Data were compared with the previously reported, less sensitive in house assay (IA; Mederacke et al., J Clin Microbiol. 2010;48, 2022–9).
Results: HDV RNA was undetectable by both, the sensitive RA and the IA in 25 (27%), 29 (31%) and 22(24%) patients at treatment weeks 48 and 96 and FU week 24, respectively. Low viremia (IA undetectable/RA positive) was detected in 15 (16%), 13 (15%) and 7 (8%) patients at these time points with very low viremia below 100 IU/ml in most cases. Low HDV viremia detectable at week 48 or week 96 was associated with a high risk for post-treatment relapse (positivity in both assays at FU week 24 in 10/15 (67%) for week 48 LV samples and 10/13 (77%) for week 96 LV samples). In contrast, the post-treatment relapse rate was lower in patients with undetectable HDV RNA in both assays during treatment (6/25 (24%) for week 48 undetectable samples and 6/29 (21%) for week 96 undetectable samples). Low HDV viremia post treatment at week 120 was not associated with biochemical hepatitis in most cases as only 2/7 patients had elevated ALT levels, one of those with a viremia of 416 IU/ml.
Conclusion: Re-testing of HIDIT-2 samples with a very sensitive commercial HDV RNA assay identified that one quarter to one third of samples being previously classified as undetectable were actually HDV RNA positive. Detection of low HDV viremia at week 48 or end of treatment was associated with a high risk for post-treatment virological relapse. Thus, future trials should use sensitive assays to determine treatment response. The clinical meaning of off-treatment low viremia requires further investigation.

SAT431

Combination drug interactions of hepatitis B virus (HBV) S-antigen transport - inhibiting oligonucleotide polymers in vitro

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Background and Aims: Current standard of care for chronic hepatitis B (CHB) can effectively inhibit viral DNA replication but fails to reduce HBsAg that suppresses the human immune system. Previously, we have identified S-antigen Transport-inhibiting Oligonucleotide Polymers (STOPs) that share structural similarity with Nucleic Acid Polymers (NAPs) but contain several novel chemical features. STOPs can reduce HBsAg secretion by potentially affecting protein trafficking from the infected cell resulting in intracellular degradation of HBsAg. In this study, inhibition of HBV DNA or HBsAg secretion by STOPs was examined in pairwise or triple combinations with nucleos(t)ides, core assembly modulators (CAMs), and HBV-specific antisense oligonucleotides (ASOs).
Method: STOPs were synthesized on ABI 394 and Expedite 8909 synthesizers using standard phosphoramidite chemistry. In vitro combination studies were performed using the HepG2-derived HBV-producing stable cell line, HepG2.2.15. STOPs and ASO's were administered by transfection using RNAiMAX. Compounds were added to cells in a checkerboard fashion and inhibition of HBV replication measured by HBV DNA or HBsAg release assays 6 days after compound addition. Data were analyzed using the Bliss-Independence model using Pritchard's MacSynergy II.
Results: In HepG2.2.15 cells STOPs exhibit potent anti-HBsAg activity with EC_{50} values in the low nanomolar range. When tested in pairwise combinations with other inhibitors, STOPs demonstrated significant synergy (synergy volume of >100 uM^2%), synergy (25–100 uM^2%) or additivity (0–25 uM^2%); no antagonistic effects were observed. Combination of STOPs and ASOs exhibited the greatest potential for synergy with compound-dependent synergy volumes ranging from 343.05 uM^2% (ALG-010133and ALG-020002) to 3.87 uM^2% (ALG-010093 and ALG-020205). Anti-HBV DNA activity was tested in STOP pairwise combinations with nucleos(t)ides and CAMs. STOPs demonstrated minor synergy with nucleos(t)ides (synergy volumes of 25.91 uM^2% and 29.01 uM^2%) and additive interactions with CAMs (1.35 uM^2%). No antagonistic effects were observed.
Conclusion: Future functional cure for CHB will require a combination of compounds with different mechanisms of action. STOPs demonstrate an in vitro antiviral profile that suggests they may become an important component of functional cure combination therapy. To this end, our STOP compounds are currently advancing towards combination clinical trials in CHB.

SAT432

Bile acid derivatives inhibit hepatitis B virus infection in vitro and in vivo

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Background and Aims: Chronic hepatitis B virus (HBV) infection remains a major health problem worldwide. Currently, the first-line treatment for HBV is nucleos(t)ide analogs or interferon (IFN); however, efficient therapeutic approaches to achieving a cure are lacking. Therefore, novel anti-HBV agents with different mechanisms from current drugs are needed. Recently, sodium taurocholate cotransporting polypeptide (NTCP) was identified as an HBV receptor, and it is strongly and negatively regulated by bile acid (BA)-activated FXR via induction of small heterodimer partner (SHP). We hypothesized that BA derivatives, which are FXR agonists, would block HBV entry efficiently by inhibiting NTCP.
Method: HepG2-hNTCP-C4 cells in which NTCP was forcibly expressed in cell lines and fresh human hepatocytes (PXB-cells) collected from chimeric mice were used to examine the efficacies of BA derivatives against HBV as *in vitro* study. HepG2.2.15 cells which were stable HBV expression cells were also used to evaluate the mechanisms of strong inhibitory effect against HBV by FXR/TGR5 dual agonist (dual agonist). We also employed uPA/SCID mice with humanized liver (PXB mice) to examine the efficacy of dual agonist against HBV infection *in vivo*.
Results: In the infection experiments of HBV with HepG2-hNTCP-C4 and PXB-cells, dual agonist showed a strong dose-dependent inhibitory effect against HBV. On the other hand, dual agonist did not show any inhibitory effect against HBV in HepG2.2.15 cells. In the binding assay between TAMRA fluorescently labeled HBV preS1 protein and NTCP on the liver cell membrane, dual agonist showed strong inhibitory effect. Dual agonist severely prolonged the initial rise of hepatitis B surface antigen (HBsAg) and hepatitis B-e antigen (HBeAg), and significantly suppressed the HBV DNA during administration in PXB mice.
Conclusion: Our results suggest that BA derivatives are prospective candidate anti-HBV agents. By analyzing in detail the mechanism of dual agonist's strong anti-HBV effects, it leads to the development of more effective and safer anti-HBV agents.

SAT433

Early on-treatment ALT normalization in patients with chronic hepatitis B is associated with lower risk of hepatocelluar carcinoma development

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Background and Aims: Recently, the use of potent antiviral agents has made it possible to effectively reduce liver disease related events such as hepatic encephalopathy, variceal bleeding, ascites, and HCC in patients with chronic hepatitis B. The aim of this study was to determine whether there is a relationship between normalized ALT resulting from the use of antiviral agents and the occurrence of liver disease related events.
Method: From 2007 to 2018, we studied 427 patients treated with entecavir or tenofovir at Korea University Guro Medical Center. The patients divided into ALT normal group and ALT abnormal group after 1 year of antiviral treatment. The ALT normal level is 34 for men, 30 for women in the KASL standard, and 35 for men and 25 for women in the AASLD standard. Liver related disease included HCC, hepatic encephalopathy, variceal bleeding, and ascites.
Results: The baseline characteristics of 427 patients median age was 50 (IQR 42~57), median value of AST was 78 (IQR 47~135), ALT was 88 (IQR 45~178), HBV DNA(IU) was 2,190,000 (IQR 170,000~36,815,316IU), and AFP was 7.05(IQR 3.325~26.025). 67% of all patients were male and 33% were female. 61.4% of patients used entecavir and 46.4% of patients used tenofovir. The people who used both drugs sequentially were 7.5%. Patients with HBeAg-positive were 54.8% and patients with anti-HBe Ab positive were 50.8%. Overall survival in ALT abnormal group was lower than ALT normal group after 1 year of antiviral treatment without statistical significance (Log rank test, $P = 0.201$ in the KASL standard and $P = 0.265$ in the AASLD standard). The cumulative incidence of HCC in normal ALT group was significantly lower than abnormal ALT group (Log rank test, $P < 0.001$ in both the KASL and AASLD standard). The incidence of Liver disease related events in the two group was not significant. (Log rank test, $P = 0.333$ in the KASL and $P = 0.428$ in AASLD standard).
Conclusion: ALT normalization after 1 year of entecavir and tenofovir treatment is correlated with reduction of development for HCC, but not overall survival and development of liver disease related events. Patients who failed to normalize ALT after 1 year of entecavir and tenofovir treatment should be observed more carefully for development of HCC.

SAT434

Best in class hepatitis B virus anti-sense oligonucleotides: next generation bridged nucleic acid chemistries significantly improve the therapeutic index by reducing hepatotoxicity and increasing in vivo efficacy in a mouse model

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Background and Aims: Reducing hepatitis B virus (HBV) S antigen (HBsAg) is key to achieving functional cure in chronic hepatitis B (CHB) patients. Antisense oligonucleotides (ASOs) are effective in reducing HBsAg in animal models, and CHB patients. However, hepatotoxicity is a major side effect of ASOs and is exacerbated with high affinity more active Locked-Nucleic Acid (LNA) modified ASOs. Next generation Bridged Nucleic Acid (BNA) and nucleobase modified monomers can reduce hepatotoxicity while maintaining efficacy. We have therefore applied these chemistries in our LNA-containing HBV targeting ASOs.
Method: ASOs with LNA and BNA chemistries were synthesized on ABI 394 and Expedite 8909 synthesizers using standard phosphoramidite chemistry. In vitro screening of LNA ASOs was carried out in HepG2.2.15 cells using a HBsAg release assay. Potent LNA-containing ASOs were chosen for N-Acetylgalactosamine (GalNac) conjugation and tested at 3 × 10 mg/kg every 3 days in the adeno-associated virus (AAV)-HBV mouse model. BNA wing and nucleobase gap modifications were applied per an in-house algorithm and compared to its all-LNA ASO.
Results: The structure activity relationship (SAR) of BNA wing and nucleobase gap modifications were explored across a set of diverse LNA ASOs. For ALG-020089, an LNA-containing ASO in the HBx region, targeting all HBV transcripts including HBx, a single replacement of a 5-methyl LNA C in the wing with 5-methyl spirocyclopropyl C improved the nadir for HBsAg by 0.5 $\log_{10}$ IU/ml while reducing serum alanine aminotransferase (ALT) by 3-fold. In ALG-020090, another HBx region LNA ASO, a single replacement of deoxy-T in the gap with 2-thio T reduced serum ALT by 30-fold to normal levels while maintaining in vivo activity. Interestingly, these

modified ASOs demonstrate equal potency to an ASO (SSO-2) currently in clinical development but eliminated the ALT elevations in mice associated with the compound. Furthermore, combination of HBsAg and HBx region ASOs demonstrated additive to synergistic antiviral activity in vitro.
Conclusion: We demonstrated that applying next generation BNA and nucleobase chemistries in LNA ASO gapmers can significantly improve the in vivo therapeutic index. A combination of HBsAg and HBx region ASOs demonstrated that these novel nucleotide chemistries could lead to best in class anti-HBV ASOs. Currently, these novel ASO therapeutics are being advanced into clinical trials for CHB.

SAT437
The establishment of hepatitis B care and treatment clinics with viral load testing capacity in the United Republic of Tanzania: a demonstration project following WHO guidelines, Dar es Salaam, 2017–2019

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Background and Aims: About 257 million persons are living with chronic hepatitis B virus (HBV) infection worldwide, which is responsible for 887,000 annual deaths. The African region has a HBV prevalence of 6.1%. To mitigate this burden, the World Health Organization (WHO) issued HBV care and treatment guidelines in 2015 for low resource countries. We report early results of the implementation of HBV care and treatment programs in Tanzania following WHO guidelines with HBV DNA testing capacity.
Method: A five year demonstration project was launched in December 2016 at Muhimbili National Hospital in Dar es Salaam. Clinical and laboratory staff at each site received training regarding the delivery of HBV-directed care and HBV-related laboratory testing. Participants were recruited from Tanzania's National Blood Donation Program where donors are systematically screened for HIV, hepatitis C, syphilis, and hepatitis B surface antigen (HBsAg). Participants were invited to participate in the program if they tested negative for HIV and HCV, and were HBsAg-positive. Participants were examined for clinical signs of liver disease and received HBV-related laboratory testing every 6–12 months for assessment of antiviral treatment eligibility by WHO criteria. Tenofovir disoproxil fumarate (TDF) was provided for treatment-eligible participants.
Results: After 34 months, 1,465 participants were enrolled: 905 with complete laboratory results, 298 with two clinic visits, and 28 with three clinic visits. Median age for patients with complete lab results was 34 years (IQR 28–42), 874 (68%) male. Of these, 144 were treatment eligible by WHO guidelines, and 81 were started on TDF. Among those treated HBV DNA values decreased significantly from a median of 28,694 (IQR 52–691,983) to 22 (IQR 20–394), $p = 0.003$, and remained stable for those not treated ($p = 0.96$); median ALT values also decreased significantly from 44 (26–116) to 27 (18–41) ($p = 0.001$). Of enrolled patients, 22 were diagnosed with hepatocellular carcinoma. Challenges included drug licensure, patient affordability of HBV-related testing, and overwhelming demand for HBV services.
Conclusion: HBV care and treatment is feasible in low-resources settings, however testing and linkage to care is critical to decrease the global burden of hepatitis B. Most persons who were treatment eligible had advanced liver disease indicating the need for HBV management in Sub-Saharan Africa.

SAT438
Solving the cold chain problem - development of a heat-stable therapeutic vaccine to combat chronic hepatitis B

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Background and Aims: The simultaneous induction of B- as well as virus-specific effector T-cell responses seems to play an important role for an effective therapeutic vaccine against chronic hepatitis B. Therefore, we developed a heterologous protein prime, modified vaccinia virus Ankara (MVA)-boost therapeutic vaccine which proved to break immune tolerance in various chronic hepatitis B mouse models. A major challenge of worldwide vaccine application is that the vaccine components require appropriate cooling during transport and storage to maintain efficacy. This is an important logistic and financial challenge in particular in low- and middle-income countries and areas with high outdoor temperatures. To prevent loss of vaccine efficacy due to thermal instability, we aimed to develop a new, lyophilized, heat-stable vaccine containing hepatitis B virus (HBV) surface (HBsAg) and core antigen (HBcAg), as well as an MVA vector expressing core and S protein (MVA-S/C).
Method: Vaccine components were formulated with stabilization and protection solutions (SPS®) platform technology. Integrity of the antigens after thermal stressing was analyzed by ELISA, Western Blot (WB), native agarose gel electrophoresis (NAGE), dynamic light scattering (DLS) and transmission electron microscopy (TEM). MVA-S/C infectivity was evaluated by $TCID_{50}$. Immunogenicity and safety of our vaccine were validated in wild-type (WT) and adeno associated virus (AAV)-HBV-transduced mice.
Results: Our *in vitro* results demonstrated a very good thermostability of the SPS®-formulated vaccine components. These stabilized components maintained antigen integrity, stability and quality as well as viral infectivity, even after a 40 °C temperature challenge for one month or a 25 °C challenge for 12 months. *In vivo* experiments in WT-mice showed that all stabilized vaccine components were very well tolerated and induced strong HBsAg-specific and HBcAg-specific $CD8^+$ T-cell response as well as high-titer HBV-specific antibodies despite the temperature stressing. Even after 12 months storage at 25 °C we could show that our stabilized vaccine was safe, able to suppress antigen levels and HBV-replication in AAV-HBV-transduced mice as well as capable of breaking immune tolerance.
Conclusion: Our results demonstrate that SPS®-formulation allows to generate a highly functional and heat-stable vaccine to combat chronic hepatitis B worldwide, especially in countries without functional cooling chains.

SAT439
Multicistronic DNA-based therapeutic vaccine as a promising candidate to treat chronic hepatitis B virus (HBV) infection

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Background and Aims: Induction of HBV-specific immune responses by therapeutic vaccination represents promising novel therapy to cure chronic HBV infection. We have developed a clinical candidate therapeutic hepatitis B vaccine (*TherVacB*), based on two protein immunizations with recombinant surface and core antigens (HBsAg, HBcAg) and a boost with Modified Vaccinia virus Ankara vector

(MVA) expressing HBV antigens. Disadvantages of very complicated and expensive purification of the recombinant proteins for clinical use could be overcome by DNA-based vaccines which lead to production of the antigens of interest directly *in vivo*. Therefore, we aimed to generate DNA vaccine covering the most common HBV genotypes and serotypes to broaden and improve B- and T-cell immune responses elicited by *TherVacB*.

Methods: Therapeutic DNA based vaccine (DNA-HBVac), encoding HBV small and large envelope proteins of genotypes A and B/C, core protein of genotypes B/C and D and HBV reverse transcriptase (RT) domain was generated. Western blotting and ELISA were used to examine stability and integrity of the expressed antigens *in vitro*. Immunogenicity of DNA-HBVac was assessed in C57BL/6 mice and AAV-HBV mouse model reflecting persistent HBV infection. HBV-specific B- and T -cell responses were determined by ELISA and flow cytometry.

Results: *In vitro* analysis showed that all DNA-HBVac-encoded HBV proteins were properly expressed. Immunization of C57BL/6 mice with DNA-HBVac prime and MVA-HBVac boost proved to be safe and well tolerated. The regimen resulted in very strong HBV-specific CD8 and CD4 T-cell responses as compared to previous immunization strategies, but as expected low anti-HBs response. Employing persistent HBV infection model, AAV-HBV-transduced mice, we could demonstrate that priming with DNA-HBVac elicited strong core-, envelope-, and RT-specific CD8 T-cell response in the livers of the mice. Moreover, we have observed significant serum ALT elevation during DNA-HBVac vaccination, suggesting increased cytotoxic T cell activity in the liver. These vigorous HBV-specific CD8 T cell responses resulted in a significant serum HBsAg and HBeAg reduction and even HBV clearance in some mice.

Conclusion: Our results show that DNA-HBVac may be a promising alternative for the classical recombinant protein priming for *TherVacB* regimen, without the need for labor intensive and expensive recombinant protein purification.

SAT440

EDP-514, a novel pangenotypic class II hepatitis B virus core inhibitor: preliminary results of a phase 1 study in healthy adult subjects

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Background and Aims: Chronic hepatitis B (CHB) is a global public health challenge with an unmet medical need for curative therapy, i.e., a finite treatment which yields a sustained post-treatment response. EDP-514 is a potent inhibitor of HBV replication with an *in vitro* EC_{50} of 18, 27 and 17 nM in HepAD38, HepDE19, and HepG2.2.15 cells, respectively, and a >4-log viral load reduction in HBV-infected chimeric mice with human liver cells. Here, we present preliminary pharmacokinetic (PK) and safety results of single ascending doses (SAD) of EDP-514 from an ongoing SAD and multiple ascending dose (MAD) phase 1 study in healthy subjects (HS).

Method: A randomized, double-blind, placebo (PBO)-controlled study is being conducted to characterize the safety and PK profile of SAD and MAD, and food effect (FE) in HS. Fifty subjects (EDP-514 [n = 38] or PBO [n = 12]) were enrolled into 6 SAD cohorts (Table 1); in the MAD phase, 32 subjects are planned to receive either EDP-514 (n = 24) or PBO (n = 8).

Results: The blinded safety data demonstrate that adverse events (AEs) were infrequent, mild in intensity, and with no severe or serious AEs, and no AEs that led to study drug discontinuation. Only the event of mild headache was observed in 4 subjects and resolved in follow-up. No clinically significant laboratory test abnormalities or pattern of abnormalities was observed.

Based on preliminary PK results, EDP-514 exposure increased with increasing single doses in an approximately dose-proportional manner, up to 600 mg (Table 1). The mean plasma concentration at 24 hr ranged from 2.4- to 10.7-fold higher than the *in vitro* serum protein adjusted EC_{50} of 71 ng/mL.

Conclusion: In the SAD phase, EDP-514/PBO was generally safe and well-tolerated, with favourable PK exposures supporting once daily dosing. Further data from MAD cohorts in HS will be presented.

SAT441

Novel cell culture 3D model for HBV/HIV co-infection and antiviral evaluation

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Background and Aims: The impact of prior HIV-1 infection on the development of chronic hepatitis B infection accelerates progression of HBV-related liver disease, increases persistent infection, risk of hepatocellular carcinoma, and liver-related mortality; It also increases HBV DNA levels and lowers HBeAg loss and $CD4^+$T cells. A relevant *in vitro* model should be able to quantify these effects as well as the impact of novel antivirals on these events. Our objective was to develop a 3D model that mimics native tissue environment, allowing co-culture and maintenance of phenotype and function.

Method: Using magnetized cells with nanoshuttle bioprinting solution, we built organoids with HepAD38 or HepG2-NTCP cells with or without $CD4^+$T cells. Cells were infected with HBV (for HepG2-NTCP) or HIV-1 (for $CD4^+$ T cells). We measured p24 antigen (ELISA) and HIV-1 RNA (RT-PCR) for HIV-1, and HBeAg (ELISA) and HBV DNA and cccDNA (qPCR) for HBV. We assessed a panel of antiviral drugs including tenofovir alafenamide (TAF), entecavir (ETV) and our HBV capsid assembly modulator (GLP-26 – AAC, PMID: 31712213, 2019) in this organoid system.

Results: Novel 3D co-cultured organoids were created and permissive to HBV/HIV-1 infection. Immunofluorescence confirmed the presence of HIV-1 (p24 antigen) and/or HBV (core antigen) in these organoids (Fig.1). No apparent cytotoxicity was observed on both cell types when they were co-cultured with or without HIV-1. HepG2-NTCP plus $CD4^+$T cells secreted HIV-1 p24 antigen and were positive for HIV-1 RNA. Presence of HIV-1 in co-cultured organoids did not

Table: (abstract: SAT440): Preliminary PK results of EDP-514 in the SAD phase

Dose (mg)	$AUC_{0\text{-inf}}$ (ng/mL*hr)	C_{max} (ng/mL)	C_{24} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)
50	10588 (30.2)	559 (18.2)	171 (37.3)	3 (1–5)	17.2 (9.1)
100	16388 (26.1)	876 (41.8)	239 (32.5)	3 (1–5)	25.2 (39.6)
200	19962 (18.6)	1030 (20.3)	338 (28.9)	3.5 (2–4)	15.6 (15.9)
400	34194 (36.6)	2244 (45.4)	490 (38.4)	3 (2–4)	18.3 (39.3)
400 – fed	57177 (18.3)	3420 (21.5)	1063 (34.9)	6 (5–10)	15.1 (19.2)
600	55035 (31.0)	2978 (37.1)	757 (30.3)	2.5 (2–3)	20.3 (44.4)
800	53701 (34.7)	2558 (25.4)	647 (32.4)	2 (1–5)	28.7 (45.5)

Data presented as mean (%CV) except for T_{max} (median [range]); Doses were given fasted except as indicated.

increase levels of HBV DNA or cccDNA. TAF or ETV inhibited HIV-1 RNA replication in co-cultured and coinfected cells. TAF, ETV or GLP-26 similarly inhibited HBV DNA replication in HepAD38 cells mono- or -cocultured with $CD4^+$T cells, with or without HIV-1. GLP-26 in the presence or absence of HIV-1 inhibited HBV DNA replication more potently than TAF or ETV, with EC_{90} values 3- to 7-fold lower for GLP-26 *versus* TAF or ETV.

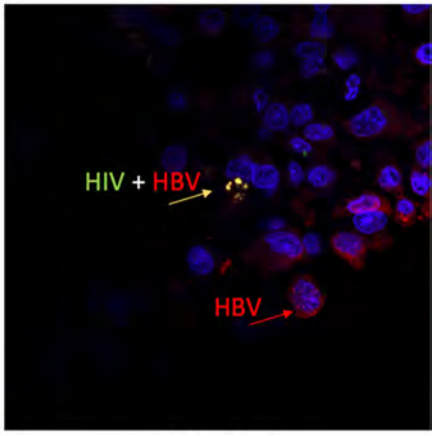

Figure 1: Immunofluorescence image of 3D co-cultured HepAD38 plus $CD4^+$T cells co-infected with HIV-1.

Conclusions: Organoids contained HBV (HepAD38 or HepG2-NTCP) and HIV-1 ($CD4^+$T) permissive cells supported productive HBV and/or HIV-1 replication. This novel model was reproducible and provided multiple and simultaneous modalities to quantify HIV-1 and HBV replication; this system can be used to measure key cellular events that drive pathogenesis of HIV-1/HBV in co-infected individuals, and can also be used to identify novel agents that block these events in the context of a relevant cellular system of co-infection. More importantly, we validated this novel organoid system of co-infection as a model for HBV infection and antiviral evaluation.

SAT442

Safety and efficacy of switching to tenofovir alafenamide (TAF) in virally suppressed chronic hepatitis B (CHB) patients with hepatic impairment: week 48 results from a phase 2 open label study

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Background and Aims: Switching to TAF, a novel tenofovir prodrug, has shown maintenance of viral suppression with stable or improved bone and renal safety at Wk 24 in CHB patients with impaired hepatic function. Here we evaluated the efficacy and safety 48 weeks after CHB patients with hepatic decompensation were switched to TAF.
Method: In this Phase 2 study (NCT03180619) patients with CHB having a Child–Turcotte–Pugh (CTP) score ≥7 and ≤12 at screening, or by documented history, receiving TDF and/or other OAVs for ≥48 weeks, with HBV DNA <LLOQ for ≥24 weeks and <20 IU/mL at screening were eligible to participate. All patients were switched to TAF 25 mg QD and were to be treated for 96 weeks. Safety assessments including changes in bone (hip and spine BMD) and renal (CrCl by Cockcroft-Gault [$eGFR_{CG}$], serum creatinine) parameters, viral suppression, and biochemical responses were assessed at Week 48.
Results: 31 patients were enrolled at 18 sites in 7 countries and 90% completed 48 weeks of treatment. At baseline, 74% were ≥50 y, 68% male, 81% Asian, 90% HBeAg-negative, with median fibrotest (FT) score 0.81, median CTP and MELD scores of 6 and 10, respectively, median $eGFR_{CG}$ 98 mL/min, and 19% and had osteoporosis by T score at spine. Prior use of TDF and entecavir was reported by 68% and 45%, respectively. Key efficacy/safety results at Week 48 are summarized in the Table. By missing equals failure analysis, 31 patients (100%) had HBV DNA <20 IU/mL, 81% had normal ALT and CTP/MELD scores were stable. After switching to TAF in this population with liver impairment, CTP, MELD, and FT scores were unchanged while bone and renal parameters were stable. TAF was well tolerated with few having Grade 3 or 4 AEs (4 patients); no serious AEs related to study drug, and 1 patient who discontinued for worsening renal function unrelated to TAF.
Conclusion: CHB patients with hepatic impairment who were switched to TAF from TDF or other OAV showed high rates of viral suppression, normal ALT and bone and renal safety were stable at Week 48.

SAT443

Prospective evaluation of qHBsAg decline in patients affected by chronic hepatitis B, E genotype, treated with entecavir or tenofovir

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Background and Aims: European clinical practice guidelines (EASL) on chronic hepatitis B recently recognized the importance of migration flows in changing the prevalence and incidence of hepatitis B infection in low endemic European countries such as Italy and Germany. Phylogenetic analyses have shown that genotype E, which is mainly diffused in West Africa, is relatively recent. No data were available about a different serological or virological response in naïve patients affected by chronic hepatitis B (CHB), E genotype treated with tenofovir (TDF) or ETV. The aim of this study was the prospective evaluation of serological and virological response in a cohort of CHB patients with E genotype treated with TDF or ETV and followed for at least 5 years.
Method: we prospectively evaluated qHBsAg decline in chronic hepatitis B, HBeAg-negative, E genotype, treated with tenofovir 245 mg (TDF) or ETV 0.5 mg from 2008 to 2014. Inclusion criteria were: naïve patients with active chronic hepatitis B (CHB) without other viral co-infection. qHBsAg test was performed with ARCHITECT HBsAg (Abbott Diagnostics, Ireland). Serum HBV-DNA levels were quantified by the Real Time PCR COBAS AmpliPrep/COBAS TaqMan HBV Test 2.0 (Roche Molecular Systems, NJ, USA).
Results: sixty-five patients (89.2% males) were enrolled. Median age was 29 years [IQR 22–36] and the most prevalent route of transmission was familiar (25; 38.5%). Median liver stiffness was 7.4 kPa [IQR 4.5–9.3], ALT 65 U/L [IQR 31–122], HBV-DNA 3.4Log IU/ml [IQR 2.8–4.5], qHBsAg3.4Log UI/ml [IQR 2.8–4.5]. According to clinical evaluation, 40 patients (61.5%) started ETV whereas 25

Table. Efficacy and Safety Results at Week 48

n/N (%), or median (Q1, Q3)	TAF (N=31)
Efficacy	
HBV DNA <20 IU/mL[a]	31 (100)
ALT normal (2018 AASLD criteria)[a,b,c]	25 (81)
ALT normalization (2018 AASLD criteria)[a,d]	6/10 (60)
HBeAg loss[a,e]	0/3
HBsAg loss[a]	1/30 (3)
qHBsAg, log_{10} change (IU/mL)	-0.07 (-0.11, -0.02)
CTP score change	0 (-1, 0)
MELD score change	0 (-1.1, 1.1)
Bone safety	
Hip BMD, % change	-0.19 (-1.515, 1.635)
Spine BMD, % change	+0.95 (-1.461, 1.933)
CTX, % change (ng/mL)[f]	-8.9 (-21.4, 5.3)
P1NP, % change (ng/mL)[g]	3.11 (-23.25, 26.50)
Renal safety	
sCr, change mg/dL	0.01 (-0.07, 0.13)
$eGFR_{CG}$, mL/min	-0.2 (-14.4, 4.2)
RBP/Cr, % change[h]	-20.7 (-50.5, 4.2)
β2MG/Cr, % change[i]	-22.7 (-65.3, 11.4)

[a]Results are by missing=failure analysis and reported as median (Q1, Q3) unless otherwise stated.
[b]ALT normal is the proportion with ALT ≤ULN at Week 48, regardless of ALT level at baseline;
[c]ULN 35 U/L males, 25 U/L females; [d]Patients with ALT >ULN at baseline;
[e]HBeAg-positive at baseline. [f]Serum C-type collagen sequence (bone resorption marker); [g]Serum procollagen type I N-terminal propeptide (bone formation marker); [h]Urine retinol binding protein/creatinine (tubular marker); [i]Urine beta-2 microglobulin/creatinine (tubular marker). BMD, bone mineral density by DXA scan; sCr, serum creatinine; $eGFR_{CG}$, estimated creatinine clearance (Cockcroft-Gault method).

Figure: (abstract: SAT442)

patients (38.5%) TDF. The qHBsAg decline was significantly higher in patients treated with TDF at any time-points and after 5 years the median decline with ETV was 0.31 LogIU/mL and 0.68 LogIU/mL with TDF. At the same time-points higher response rate in HBV-DNA suppression were observed in patients receiving TDF. In the absence of resistance-associated mutations, in 20% of ETV-patients HBV-DNA persisted detectable at 5 years. In univariate analysis for qHBsAg decline the following factors were considered: age, sex, qHBsAg and HBV-DNA at baseline, liver stiffness, type of therapy. In the multivariate analysis the only predictive factor for qHBsAg decline is the treatment with TDF ($\beta = -0.119$; DS = 0.025; $p < 0.001$).
Figure: qHBsAg decline after 5 years of therapy in patients affected by CHB and treated with ETV or TDF.
Conclusion: in E genotype the patients treated with TDF showed greater qHBsAg decrease after 5 years than ETV; virological response was higher in TDF than ETV groups. The reason of this finding was unknown and further studies are required to explain this aspect. According to our results, however, TDF could represent the optimal choice in this setting of patients.

SAT444

Low HBcrAg and HBsAg levels identify patients most likely to achieve sustained response after nucleos(t)ide analogue cessation: results from a global individual patient data meta-analysis (create study)

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Background and Aims: Sustained response is observed in a limited number of patients after cessation of nucleo(s)tide analogue (NA) therapy. We aimed to study the relationship between serum levels of hepatitis B core related antigen (HBcrAg) and HBsAg at treatment

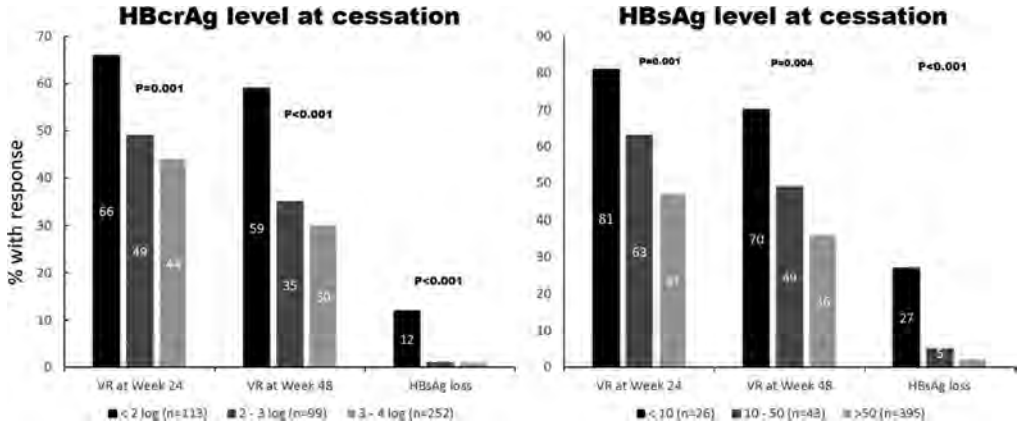

Figure: (abstract: SAT444): Observed response rates across HBcrAg and HBsAg level at treatment cessation. VR: virological response.

cessation and subsequent sustained virological response and HBsAg loss.

Method: We performed an individual patient data meta-analysis of patients who discontinued NA therapy in compliance with EASL criteria. Patient data was acquired from 9 cohorts from Asia and Europe. HBcrAg and HBsAg were measured at treatment cessation. Studied endpoints included virological response (VR, defined as HBV DNA <2,000 IU/mL) and HBsAg loss at 24 and 48 weeks off-treatment. Retreatment was based on HBV DNA and ALT criteria, and retreated patients were considered non-responders.

Results: We analysed 464 patients, of whom 317 (68%) were male and 75 (16%) were HBeAg positive at the time of treatment initiation. Median treatment duration was 294 weeks (IQR: 196–428), and median duration of consolidation therapy was 102 weeks (IQR: 56–165). Patients were treated with ETV/TDF/other in 61%/27%/12%. VR was observed in 234/464 (50%) at week 24 and 155/401 (39%) at week 48 post-treatment. HBsAg loss was observed in 17 (4%) patients. 216 patients were retreated during the follow-up period, with HBV DNA elevation (76%) and ALT flare (21%) the main indications. All resolved without sequelae after retreatment. VR at week 24 was observed in 74/113 (66%) of patients with HBcrAg <2 log at treatment cessation, compared to 44% in patients with HBcrAg >3 log (p = 0.001; figure 1). Similar results were observed at post-treatment week 48. HBsAg loss was observed in 12% of patients with HBcrAg <2 log at treatment cessation, versus 1% in patients with HBcrAg >3 log (p < 0.001). Similarly, VR at week 24 was observed in 21/26 (81%) of patients with HBsAg <10 IU/mL, versus 47% in patients with HBsAg >50 IU/mL (p = 0.001) at treatment cessation. Similar results were obtained when response was assessed at post-treatment week 48. HBsAg loss was observed in 27% of patients with HBsAg <10 IU/mL at treatment cessation, versus 2% in patients with HBsAg >50 IU/mL (p < 0.001). Findings were consistent when limited to the subset of patients who were HBeAg-negative at start of NA therapy.

Conclusion: In this global individual patient data meta-analysis of patients who discontinued NA therapy, low HBcrAg (<2 log) and low HBsAg levels (<50 IU/mL) at treatment cessation were associated with highest rates of VR and HBsAg loss. These cut-offs could be used for an improved selection of patients for NA cessation.

SAT445

Silencing HBV expression using LNA gapmers: preliminary data of a new promising strategy

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Background and Aims: A low but relevant percentage of successfully treated patients with chronic Hepatitis B develop hepatocellular carcinoma due to the continuous intrahepatic expression of viral proteins. A therapy based on gene silencing could be a useful approach in these cases, and the X gene (HBX), thanks to its co-terminal localization, could be an optimal target. Here we presented a new system of gene silencing based on antisense locked nucleic acid (LNA) Gapmer that targets some hyper-conserved regions of HBX.

Method: HepG2-NTCPs were treated with DMSO 2.5% at least 14 days. They were infected with Hepatitis B virus (HBV) at multiplicities of genome equivalents of 250–500 by 1 hour (h) of spinoculation at 37°C followed by a maximum of 24 h of incubation. At 48 h post infection cells were transfected, using TransIT-X2, with 4 different antisense LNA Gapmers (GP1 to 4) from 12.5 to 100nM. Cells and supernatants were collected at 72 h post treatment. Extracellular HBV e antigen (HBeAg) and s antigen (HBsAg) were quantified using a chemiluminescent immunoassay (CLIA). Intracellular RNA was extracted using RNeasy micro kit and pregenomic RNA (pgRNA) was quantified by RT-qPCR using Taqman probe. A scrambled control Gapmer was included in each experiment.

Results: At the lowest concentration tested, GP1 and GP4 efficiently inhibited HBeAg expression (respectively 68.6 and 54.8% of inhibition related to the mock-untreated). At 50nM the reduction related to the scramble was 68.9 and 53% for HBeAg and 76.8 and 62% for HBsAg. The association of GP1+GP4 and GP2+GP3 did not increase the inhibition of viral protein expression (respectively 60.5 and 24.4% for HBeAg and 65.4 and 28.1% for HBsAg). Mock-untreated HBV infected cells actively produced pgRNA reaching an amount of 4 log of copies/ng of total RNA. GP treatment induced a reduction of pgRNA, related to the scramble, of 76.2, 69.3, 66.3 and 31.4% in presence of GP1, GP4, GP1+4 and GP2+3 respectively (from 1 to 0.6 log less related to the mock-untreated). Of note, pgRNA and HBeAg production strongly correlated (p < 0.001, rho = 0.9).

Conclusion: HBeAg could to be an optimal *in vitro* marker of productive HBV replication. LNA Gapmers efficiently inhibit the viral expression. Considering their ability to entry into cellular nucleus, they could be a new valuable therapeutic strategy to control the intracellular expression of HBV. Further experiments are required to confirm these preliminary data and improve Gapmer efficiency.

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SAT446

The composition of HBsAg during peginterferon-alfa2a treatment can predict treatment response in HBV/HDV-coinfection

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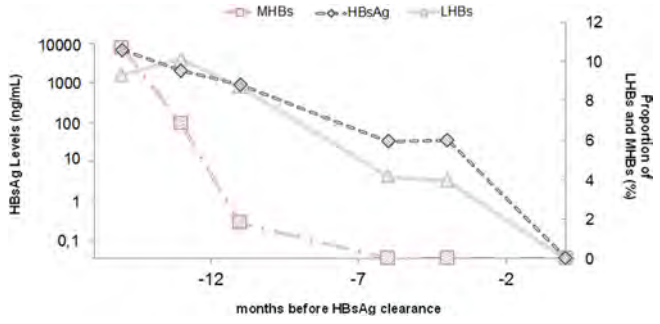
Background and Aims: Treatment with pegylated interferon alpha-2a (PEG-IFN) is currently considered the standard of care for patients with HBV/HDV-coinfection, and clearance of HBsAg provides the optimal treatment end point. The proportion of the different HBsAg components (large (L), middle (M) and small (S)HBs) was shown to predict HBsAg loss in patients with HBV mono infection. Aim of this retrospective study was to assess whether the HBsAg composition before and during treatment may also be associated with HBsAg clearance in patients with HBV/HDV-coinfection.

Method: A total of 26 Patients received 180 mg PEG-IFN per week for a mean time of 40.7 (9–100) months. HBV biomarkers including HDV RNA, HBV DNA, HBV RNA and HBsAg components were measured in available serum samples.

Results: During treatment, 4/26 patients showed HDV RNA loss and HBsAg clearance whereas 22/26 patients showed no serological response (NR), from whom 6/22 achieved undetectable HDV RNA levels. HDV RNA (mean 5.9 vs 7.8 log cp/mL; $p = 0.506$), HBV DNA (mean 3.7 vs. 3.1 log IU/mL); $p = 0.350$); HBsAg (mean 4.3 vs 4.4 log ng/mL; $p = 0.521$) and HBsAg components (mean percentages 6.6 vs 5.9 LHBs %, $p = 0.800$; MHBs 8.9 vs 13.4 %, $p = 0.521$) at baseline showed no significant difference across responders and non-responders. HDV RNA became undetectable in patients with subsequent HBsAg loss after 12 (4–24) months but showed no significant decline in the NR group. HBV DNA became undetectable in both groups. HBV RNA was undetectable in all patients and samples before and during treatment. In patients with HBsAg loss, total HBsAg levels and ratios of LHBs showed a significant decrease by month 6 and 12 treatment in comparison to the NR group (p = 0.02 and p = 0.01). Median proportions of MHBs strongly decreased during treatment (from 10.7% [15 months before HBsAg loss] to 1.8% [11 months before HBsAg loss]) and became undetectable 6 months before the loss of LHBs and total HBsAg (see Figure). In contrast, the ratios of LHBs and MHBs showed no significant difference in the NR group during the entire observation time.



Conclusion: LHBs and MHBs might be suitable markers for monitoring the efficacy of PEG-IFN treatment and response prediction in HBV/HDV-coinfected patients. Our results need to be validated in a larger patient cohort.

SAT447

All-cause mortality and liver-related death following entecavir, tenofovir disoproxil fumarate or lamivudine therapy among treatment-naive chronic hepatitis B patients in British Columbia, Canada

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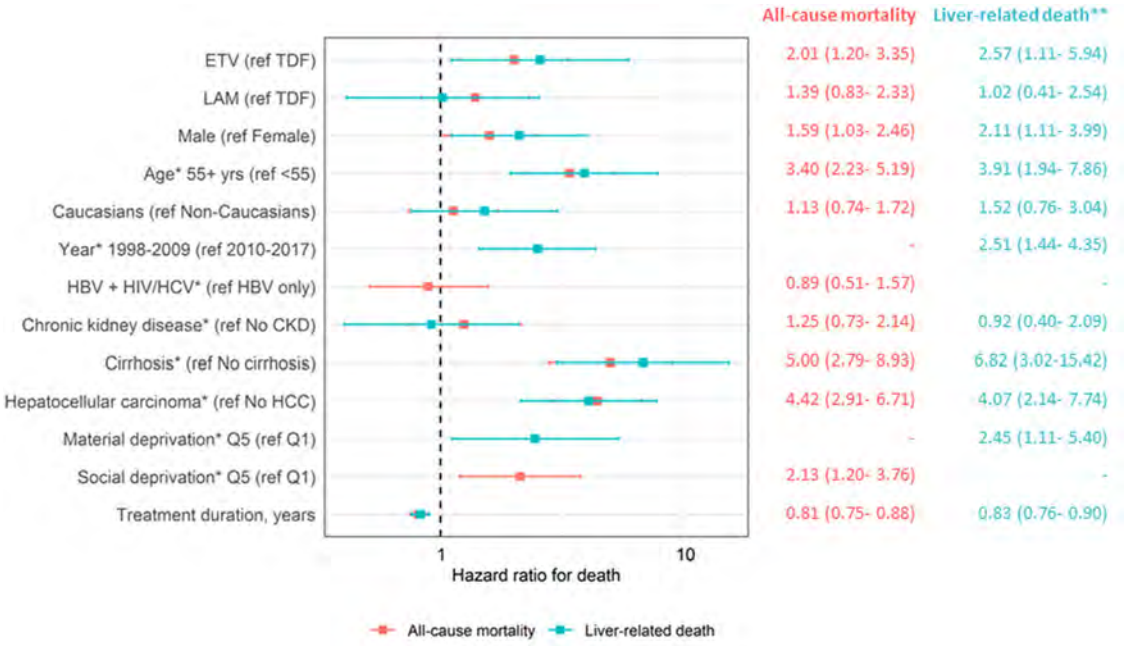
Background and Aims: Entecavir (ETV), tenofovir disoproxil fumarate (TDF) and lamivudine (LAM) are publicly-funded options for chronic hepatitis B (HBV) therapy in British Columbia (BC), Canada. Although in use for over a decade, there is conflicting information about their relative impact on long-term survival. We assessed the association between ETV, TDF or LAM therapy and all-cause mortality/liver-related death among treatment-naïve chronic HBV patients within a large population-based cohort in BC.

Method: The BC Hepatitis Testers Cohort (BC-HTC) includes data from all HBV-positive individuals diagnosed in BC from 1990–2015 linked with medical visit, prescription and mortality data. Treatment-naïve HBV-positive individuals within the BC-HTC who initiated ETV, TDF or LAM and received only one of these three drugs on or before Dec 31, 2017 were included in this study. To account for differing profiles at baseline, treatment groups were matched 1:3:3 by common referent propensity score matching with ETV as the reference group. Key matching variables included sex, ethnicity, age group, chronic kidney disease, cirrhosis and hepatocellular carcinoma at treatment start, as well as treatment duration. The relative impact of ETV, TDF, and LAM therapy on all-cause and liver-related mortality from treatment start until Dec 31, 2018 was assessed with multivariable Cox proportional-hazards models, accounting for the competing risk of death from other causes when assessing liver-related death.

Results: 2,464 matched participants initiated ETV (n = 352), TDF (n = 1,056) or LAM (n = 1,056). These individuals were mostly East Asian (63.4%), Caucasian (26.2%) and South Asian (4.4%). Relative to TDF, the ETV treatment group was at greater risk of both all-cause (adjusted hazard ratio[aHR] 2.01, 95% CI: 1.20–3.35) and liver-related mortality (aHR 2.57, 95% CI: 1.11–5.94). Differences in mortality risk for LAM and TDF treatment groups were not statistically significant (aHR: All-cause mortality 1.39, 95% CI: 0.83–2.33; Liver-related death 1.02, 95% CI: 0.41–2.54).

Conclusion: Among treatment-naïve chronic HBV patients, the risk of all-cause mortality and liver-related death post-treatment initiation was higher with ETV relative to TDF and LAM. This finding is noteworthy and warrants further study given the potential implications for HBV therapy and the conflicting findings of similar studies conducted in distinct, more ethnically homogenous, South Korean study populations.



*At HBV treatment initiation; **Competing risk: death from non-liver-related causes; LAM: Lamivudine; ETV: Entecavir; TDF: Tenofovir disoproxil fumarate; CKD: chronic kidney disease; HCC: hepatocellular carcinoma; Q: quintile

Figure: (abstract: SAT447)

SAT448

Differential tenofovir alafenamide (TAF) adoption in HBV-infected populations; assessment of care in US clinical practice

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Background and Aims: Previously we reported increased HBV suppression, ALT normalization, and improved renal function with TAF treatment. However, certain patients that would potentially benefit from switching to TAF, e.g. with impaired renal function, remained on non-TAF therapies. Here we further examined variables associated with TAF adoption from approval (Nov 2016) to Dec 2018.
Method: Patients enrolled in the TRIO HBV registry from 6 academic and 4 community centers in the US were included in this study. TAF initiation was assessed using Kaplan-Meier methods with subsequent log-rank tests. Overall TAF initiation rates were compared using z-tests.
Results: Study population (n = 1037): predominantly male (599, 58%), Asian (887, 86%), <60 years old (700, 68%), from academic centers (611, 59%), with HBV DNA suppression (951/1035, 92%), and receiving tenofovir disoproxil fumarate (TDF [640, 62%]) at enrollment. A history of HCC (inactive) was present for 2% (25) patients, 4% (44) fatty liver, 10% (103) diabetes, 13% (131) hyperlipidemia, 23% (237) hypertension, and 8% (78) osteopenia/osteoporosis. At enrollment, 5% (48/965) had FIB4 >3.25, 6% (65/1030) had eGFR <60 ml/min, and 29% (304/1035) had elevated ALT (>25 U/L in females or >35 U/L in males). In the study window, 396 (38%) patients initiated TAF. Adoption was significantly higher in patients receiving TDF at enrollment (52% v. 12% non-TDF, $p < 0.001$), at community practices (56% v. 25% academic, $p < 0.001$), and without HCC history (39% v. 8%, $p = 0.005$), fatty liver (39% v. 8%, $p < 0.001$), or hyperlipidemia (39% v. 28%, $p = 0.005$). Adoption was not significantly different by age, insurance type, osteopenia/osteoporosis, eGFR, FIB4, or ALT. [Figure] Reasons for initiating TAF were provided for 365/396 patients: 66% (241/365) indicated safety/side effects, 27% (99/365) physician preference, and 6% (21/365) efficacy.
Conclusion: Safety/side effects was stated as a primary reason for initiating TAF, yet osteopenia/osteoporosis, suboptimal eGFR, ALT, or FIB4 were not associated with significantly higher TAF adoption. These data suggest that prevention, rather than observation of detrimental clinical measures, accounted for most TAF adoption. Most patients with renal or bone disease were not switched to TAF which may be due to access, an issue which will be further explored.

SAT449

Structural requirements for S-antigen transport-inhibiting oligonucleotide polymer inhibition of hepatitis B surface antigen secretion

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FIGURE: TAF initiation in study population and by select characteristics at enrollment. X axis = months from enrollment (Nov 2016), Y axis = cumulative proportion of patients initiating TAF.

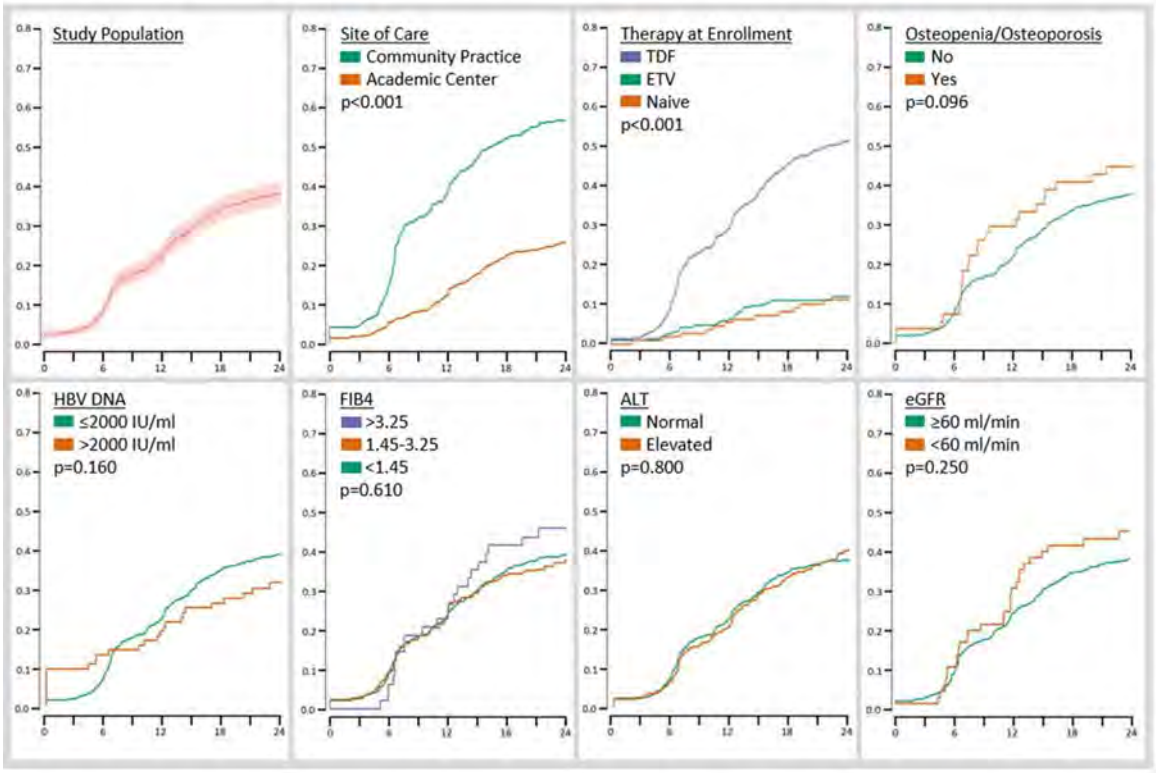

Figure: (abstract: SAT448)

Background and Aims: A functional cure for chronic hepatitis B is unavailable, as current therapeutics lack mechanisms for viral surface antigen (HBsAg) reduction. S-antigen Transport-inhibiting Oligonucleotide Polymers (STOPs) reduce HBsAg in vitro and are structurally similar to nucleic acid polymers (NAPs). Novel chemical properties have imparted 20 to 100-fold improvements in potency over clinical stage NAPs. To identify the mechanism for enhanced potency, we investigated the structural features necessary for STOPs antiviral activity via modifications of sequence, length and chemistry.
Method: To assess STOPs antiviral activity, HBsAg levels were measured in treated and untreated HBV-infected cells. Briefly, STOPs were transfected into HepG2.2.15 and HBV-infected HepG2-NTCP cells. HBsAg levels and cytotoxicity were measured 6 days post transfection via ELISA and CellTiter Glo, respectively.
Results: ALG-010000 was identified as a potent inhibitor of HBsAg secretion in HepG2.2.15 and infected HepG2-NTCP cells with EC50 values of 4.6 and 5.3 nM respectively. Varying the length of STOPs from 18–50 nucleotides (nt) revealed a length dependency on antiviral activity; potency was maintained at lengths >34 nt, and dramatically reduced at lengths <30 nt. Sequence variations in STOPs were also tested for activity. When the AC dinucleotide repeat of ALG-010000 was changed to alternative repeated bases such as AG, the antiviral activity was completely abolished. Similarly, polyA and polyC sequences were inactive, in contrast to the reported activity for NAPs. However, when the base identities were maintained, such as with a CA repeat, activity was similar to ALG-010000. Interestingly, when the optimal length was maintained, polyA stretches replacing 2–5 dinucleotide repeats at the flanks of the oligonucleotide were tolerated while polyC stretches were not. In addition to length and sequence, backbone and sugar chemistry were modified. Potency was improved with site specific incorporation of backbone chemistries such as a stereospecific phosphorothioate bond.
Conclusion: We have demonstrated that STOPs potency is length and sequence dependent, requiring a minimal length of 34 nt and a minimal AC dinucleotide composition of 50%. Chemistries that improve antiviral activity have also been identified. Collectively, these defined structural elements provide a framework for STOPs design and are important for their advancement. Further exploration is ongoing.

SAT450

Low hepatitis B surface antigen at baseline and increased ALT levels during treatment predicts significant HBsAg decline in peginterferon alfa added to long-term nucleus(t)ice analogue. Results from two randomized controlled trials in 165 patients

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Background and Aims: Pegylated-interferon (PEG-IFN) treatment has been associated with higher HBsAg decline rates than nucleos(t)ide analogues (NA) and is thus increasingly used in the setting of

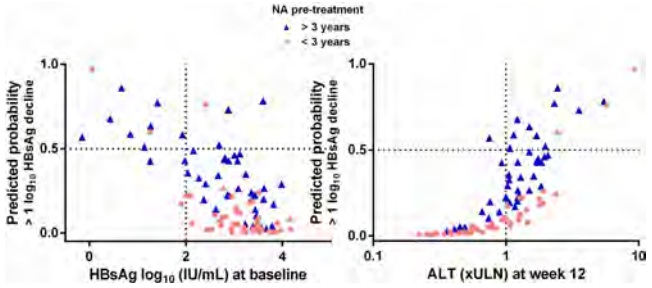
novel combination regimens aiming for functional cure. We investigated in two randomized, controlled trials the factors that influence HBsAg decline in CHB patients pre-treated with nucleos(t)ide analogues (NA) who received PEG-IFN add-on therapy.

Method: HBsAg decline was evaluated in two investigator-initiated randomized controlled trials conducted in Europe, China and Canada (PAS and PEGON studies). HBeAg positive and negative patients with normal ALT at baseline, were pre-treated with NA therapy >12 months and then were allocated to 48 weeks of NA+PEG-IFN add-on, or continued NA monotherapy. To study the factors that influence >1log$_{10}$ HBsAg decline, we performed a logistic regression analysis.

Results: Of the 165 patients, 97 (59%) patients randomized to PEG-IFN add-on, and 68 (41%) to continue NA monotherapy. At baseline, 77 patients were HBeAg positive, and 88 were HBeAg negative. The mean age was 42 years, 82% male, 79% Asian, and 17% Caucasian. The median baseline HBsAg level was 3.1 log$_{10}$ IU/mL. At week 48, 22 (13%) patients achieved HBsAg >1 log$_{10}$ decline in the add-on arm compared to none on NA monotherapy.

By univariable analysis, factors associated with >1log$_{10}$ HBsAg decline were PEG-IFN add-on (odds ratio [OR] 2.1; 95% CI 1.1–4.4; p = 0.03), HBeAg negative (OR 3.3; 95% CI 1.25–10; p = 0.02), lower HBsAg levels at baseline (OR 0.4; 95% CI 0.2–0.7; p = 0.001), longer duration (years) of NA treatment prior to Peg-IFN (OR 1.2; 95% CI 1.02–1.32; p = 0.02), and ALT (>xULN) increase during treatment starting from week 12 (OR 2.6; 95% CI 1.3–5.2; p = 0.008).

In multivariable analysis, lower HBsAg level at baseline (OR 0.3; 95% CI 0.1-0.8; p = 0.02) and ALT increase at week 12 (OR 2.5; 95% CI 1.3-4.8; p = 0.01) remained independently associated with >1log$_{10}$ HBsAg decline in patients treated with 3 years of NA or more (OR 4.2; 95% CI 1.5–12.1; P = 0.007) (figure), when adjusted for PEG-IFN add-on and HBeAg at baseline.



Conclusion: HBsAg decline >1log$_{10}$ after the addition of PEG-IFN to long term NA is significantly associated with lower levels of HBsAg level at baseline and higher ALT at week 12. Longer duration of NA therapy before PEG-IFN increases the probability of HBsAg decline.

SAT451

Efficacy and safety of switching to tenofovir alafenamide for chronic hepatitis B patients with advanced fibrosis and partial virologic response to oral nucleos(t)ide analogues (ESTAB-AFPVR) - an interim report

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Background and Aims: There were insufficient data regarding the treatment strategy for patients who demonstrated a partial or suboptimal response to entecavir (ETV) or tenofovir disoproxil fumarate (TDF). We aim to investigate the effect and safety of tenofovir alafenamide (TAF) switching in chronic hepatitis B (CHB) patients with advanced fibrosis and partial response to other nucleot(s)ide analogue (NUC).

Method: Approximately 80 adult CHB patients with advanced fibrosis (including fibrosis stage 3 and cirrhosis), who are currently on NUC (except TAF) therapy with detectable hepatitis B virus (HBV) DNA after at least 52 weeks of therapy will be considered eligible for this open label, prospective interventional cohort study. Enrolled patients will switch prior NUC to TAF 25 mg/day for 96 weeks. The objectives are to describe the improvement of rate of viral suppression, alanine aminotransferase (ALT) normalization, and the trend in renal function, bone mineral density with TAF.

Results: From Feb. 2019, 24 patients were enrolled. Seven (29.2%) were male with a median age of 53 years old. Liver fibrosis assessment showed a median level of 10.6 kPa. The median ALT level was 23.5 U/L with ALT level within normal limit (40 U/L) in 22 (91.7%) of the patients. The median hepatitis B surface antigen and HBV DNA levels were 2,267 IU/mL and 64 IU/mL, respectively. Ten (41.7%) patients were hepatitis B e antigen positive. Two (8.3%) had YMDD mutation at enrollment. The prior NUCs included ETV in 14 (58.3%), TDF in 9 (37.5%), and lamivudine in 1 (4.2%) of the patients. The median HBV DNA level declined from 64 IU/mL at enrollment to 28.5 IU/mL at 4th week, 21 IU/mL at 12th week, and below low limit of quantification at 24th week, respectively, after TAF switching. Undetectable HBV DNA was achieved in 8/24 (33.3%), 8/18 (44.4%), and 3/4 (75.0%) patients at 4th, 12th, and 24th week, respectively (figure 1A). The rate of ALT normalization was 91.7%, 87.5%, 94.4%, and 100% at enrollment, 4th, 12th, and 24th week, respectively, after TAF switching. There were no significant changes inserum creatinine and eGFR levels from enrollment to 24th week after TAF switching (figure 1B). Only mild degrees of adverse events were found which were considered unrelated to treatment. One patient withdrew at 4th week of enrollment due to personal reason.

Conclusion: The preliminary results demonstrated the efficacy and safety of TAF switching in viral suppression for those patients with advanced fibrosis and partial virologic responses to other NUCs.

SAT452

Efficacy and safety of GLS4/ritonavir combined with entecavir in HBeAg-positive patients with chronic hepatitis B: interim results from phase 2b, multi-center study

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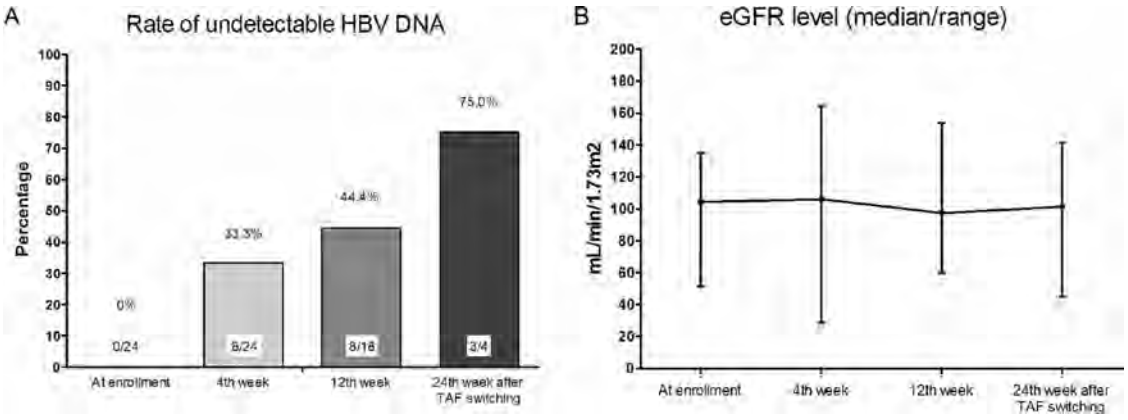

Figure: (abstract: SAT451)

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Background and Aims: GLS4 is a hepatitis B virus (HBV) capsid assembly modulator that have demonstrated potent antiviral activity as monotherapy, in this study, we evaluate the safety and efficacy of the combination therapy of GLS4/Ritonavir(RTV) with Entecavir(ETV) compared with ETV monotherapy in HBeAg positive CHB patients (pts)(Clinical trial identifier: NCT04147208).

Method: 250 CHB pts will be enrolled into 2 groups. Naïve group : treatment-naïve or patients with no prior exposure to anti-hepatitis B drugs within the last 6 months, n = 125; Virally suppressed group: patients have taken ETV for more than1 year and achieved virus suppression (HBV DNA <50 IU/mL), n = 125). In each group, pts will be randomly allocated 4:1 to receive 120 mg GLS4/100 mg RTV(TID) combined with 0.5 mg ETV(QD) or 0.5 mg ETV(QD) monotherapy for 96 weeks(assigned as cohort A and cohort B in Naïve group; as cohort C and cohort D in Suppressed group).

Results: Currently, 146 patients had been enrolled and 77 pts have received treatment≥12 weeks, available data at 12th week are presented here. Compared to baseline, mean HBV DNA reduction in treatment naïve pts were 5.02 and 3.84 log10 IU/ml, while the decline of pgRNA were 2.63 vs. 0.27 log10 IU/ml in cohort A and cohort B, respectively. For HBsAg, the mean reduction from baseline were 0.43 vs. 0.21 log10 IU/ml, and for HBeAg were 0.49 vs. 0.29 log10 IU/ml respectively in cohort A and cohort B. 28.6% pts (4/14) in cohort A and 5.9% (1/17) in cohort B had HBsAg levels declined ≧0.5log IU/ml. In cohort A, 2 pts (14.3%) had HBsAg declined ≧1.5log IU/ml (81250 dropped to 2490 IU/ml; 55620 dropped to 1760 IU/ml, respectively). In Suppressed group, the mean declines of HBV pgRNA were 1.59 vs. 0.15 log10 IU/ml in cohort C and cohort D, those of HBsAg and HBeAg were 0.11 vs. 0 log10 IU/ml and 0.17 vs. 0.06 log10 IU/ml. The proportion of HBsAg declined ≧0.1log IU/ml from baseline was 62.5% (15/24) vs. 13.6% (3/22) in cohort C and cohort D, respectively. Combination of GLS4/RTV with ETV had been generally safe and well tolerated, the most common adverse events (AEs) were ALT elevation and hypertriglyceridemia. According to CTCAE5.0, ALT elevation ≧grade 3 were 7.1%(3/42) vs. 2.6%(1/39) in GLS4/RTV+ETV combined and ETV monotherapy group, respectively. These patients'ALT level declined after temporary suspension of the drug and symptomatic treatment, and these ALT flares correlated well with more rapid decline in HBsAg and/or HBeAg. Hypertriglyceridemia ≧ grade 3 were 4.8%(2/42) vs. 0 (0/39) in GLS4/RTV+ETV combined and ETV monotherapy group.

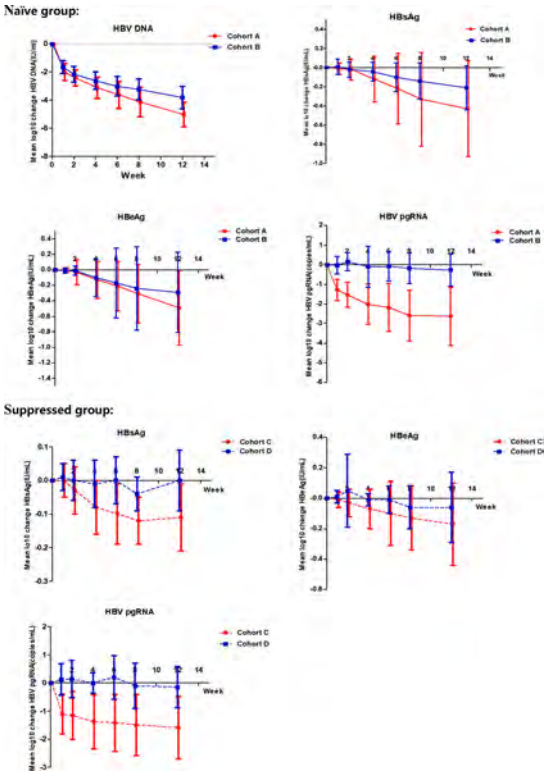

Figure: Comparison of antiviral activities between combination therapy and monotherapy.

Conclusion: Interim results showed that the antiviral efficacy of combination therapy of GLS4/RTV with ETV is remarkably superior to ETV monotherapy, further studies are ongoing to evaluate the safety and efficacy of the combination therapy.

SAT453

Long-term efficacy of generic antiviral drugs (tenofovir and entecavir) in supression of viral replication in chronic hepatitis B

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Background and Aims: The main goal of nucleot(s)ides analogues therapy in chronic hepatitis B, is to achieve sustained suppression of viral replication (VR). Antiviral therapy with Viread® (tenofovir disoproxil fumarate TDF) or Baraclude® (entecavir ETV) suppresses hepatitis B virus (HBV) viremia in most patients. The approval and commercialization of generic drugs of ETV and TDF, has resulted (since April 2017), in a change of antiviral treatment in patients previously treated with Viread® and Baraclude®, who were switched to their respective generic drugs.
The aim of our study was to assess the efficacy in suppression HBV DNA to undetectable levels of the generic antiviral TDF and ETV drugs, in patients with sustained virological response previously obtained with Viread® and Baraclude® and in patients who had been treated with generic antivirals from the beginning.
Methods: We included all chronic hepatitis B patients treated with Viread® or Baraclude® until April/2017, who were switched to generic TDF or ETV (group A) and patients who started treatment with generic antiviral drugs from the beginning, with more than 1-year follow-up (group B). Patients started on Viread® and Baraclude® after October/2016 and those with inadequate follow-up, were excluded. The follow-up protocol included viral load (VL) (HBV DNA) determination and adherence assessment, every six months. Suppression of VR was defined as undetectable HBV DNA levels.
Results: Group A: 73 patients (47 men and 26 women), with an average age of 52 years. Eleven patients were treated with Baraclude® and 62 with Viread®. Thirteen patients had liver cirrhosis and most of them (95%) were HBeAg negative. Long term virological suppression was achieved in 70 patients with Baraclude® and Viread®; after switching to generic antiviral drug, 15 of them (13 TDF, 2 ETV) showed sustained detectable HBV DNA, 4 of them were cirrhotic patients. VL ranged from 13 to 96 IU/mL.
Group B: 18 patients, 12 treated with TDF and 6 with ETV. Virological suppression was achieved in 10 patients and the remaining eight (5 TDF and 3 ETV) showed detectable VL (18–300 IU/mL) after 1-year of treatment despite a correct adherence, 3 of them were cirrhotic patients.
Conclusions: In one out five patients with chronic hepatitis B, the change of treatment from Viread® or Baraclude® to generic TDF and ETV failed to maintain VR suppression, however with viral loads below 100 IU/mL. In almost half of the patients treated with generics antiviral drugs from the beginning, therapy failed to achieve viral load suppression after more than one year of treatment. We do not know the impact of this long term incomplete viral response on the liver disease. However, in patients with cirrhosis, we have to increase the surveillance or to evaluate the use of other antiviral drugs that ensure complete VR suppression.

SAT454

Guideline change for antiviral therapy reduced the risk of HBV-related HCC development among cirrhotic patients in South Korea

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Background and Aims: In September 2015, the guideline of the Korean Association for the Study of Liver (KASL) to start antiviral therapy (AVT) for patients with chronic hepatitis B (CHB)-related cirrhosis was changed from HBV DNA level ≥2,000 IU/L and aminotransferase (AST) or alanine aminotransferase (ALT) levels ≥ upper limit of normal to HBV DNA level ≥ 2,000 IU/L regardless of the AST or ALT level. This study investigated whether the KASL guideline change reduced the risk of CHB-related hepatocellular carcinoma (HCC) development among cirrhotic patients in South Korea.
Method: A total of 429 patients with CHB-related cirrhosis who started AVT between 2014 and 2016 were recruited. The risk of HCC development was compared between patients who started AVT before and after September 2015 (previous [n = 196, 45.7%] vs. the current guideline [n = 233, 54.3%]).
Results: Univariate analysis showed that starting AVT according to previous guidelines (vs. current guideline), older age, and male gender significantly predicted an increased risk of HCC development (all $p < 0.05$). Subsequent multivariate analysis showed that starting AVT according to previous guidelines (vs. current guideline) (HR = 1.833), older age (HR = 1.041), and male gender (HR = 2.719) independently predicted an increased risk of HCC development (all $p < 0.05$). In addition, multivariate analysis showed that starting AVT according to previous guidelines (vs. current guideline) (HR = 2.400) and male gender (HR = 3.058) were independent predictors of mortality ($p < 0.05$). The cumulative incidence of HCC and mortality were significantly higher in patients who started AVT before the guideline change (all $Pp<0.05$ by log-rank test).
Conclusion: The prognosis of patients with CHB-related cirrhosis who started AVT was improved after the change in KASL guidelines.

SAT455

ALG-000184, a prodrug of capsid assembly modulator ALG-001075, demonstrates best-in-class preclinical characteristics for the treatment of chronic hepatitis B

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Background and Aims: Capsid assembly modulators (CAMs) represent a clinically validated strategy for inhibiting hepatitis B virus (HBV) RNA encapsidation, leading to reductions in circulating HBV DNA and RNA in infected patients. We recently reported on ALG-001075, a novel class-II (normal, empty capsid formed) CAM with excellent antiviral potency and in vivo efficacy in a mouse adeno-associated virus-HBV model (AASLD, 2019, poster 699). We now advance ALG-000184, a prodrug of ALG-001075, which demonstrates superior pharmacokinetic properties relative to ALG-001075.
Method: Antiviral activity on HBV DNA was determined in HepG2.117 cells using quantitative PCR, with and without 40% human serum. Activity was also assessed in primary human hepatocytes (PHH) infected with HBV. Solubility, stability and permeability of ALG-

001075 and ALG-000184 were evaluated in vitro. Pharmacokinetic properties of ALG-001075 were evaluated across species following oral dosing of ALG-001075 or ALG-000184 administered as aqueous formulations.
Results: ALG-001075 was found to be a potent inhibitor of HBV DNA production in HepG2.117 cells with EC_{50}/EC_{90} values of 0.63/3.17 nM (n = 12), a 4.2-fold shift was noted in the presence of 40% human serum. When ALG-001075 was added to PHH at the time of infection, reductions in extracellular HBsAg and HBV RNA were noted, indicating inhibition of de novo cccDNA formation. ALG-001075 has low aqueous solubility, whereas ALG-000184 showed excellent aqueous solubility (>120 mg/mL) in phosphate buffered saline (PBS) and was stable in simulated gastric or intestinal fluid ($t_{1/2}$ >12 hrs). Permeability in Caco-2 cells more than doubled and the efflux ratio was significantly reduced for the prodrug as compared to ALG-001075. When ALG-000184 was dosed as an aqueous solution in mouse, rat, monkey and dog, it was rapidly absorbed and conversion to ALG-001075 was efficient. ALG-001075 plasma exposure in rats increased linearly with ALG-000184 dosed up to 300 mg/kg, the highest dose tested.
Conclusion: ALG-001075 is the most potent class-II CAM reported to date, efficiently blocking both HBV genome encapsidation and *de novo* cccDNA formation. ALG-000184 demonstrates excellent solubility and oral absorption with efficient conversion to ALG-001075 in vivo, with pharmacokinetic properties across species predicting once daily dosing in humans. ALG-000184 is currently advancing in development as a potential best-in-class CAM.

SAT456

Longer consolidation duration is required to reduce 1-year clinical relapse rate after stopping tenofovir in HBeAg negative CHB patients

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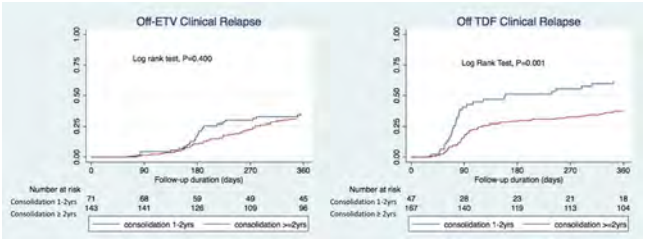
Background and Aims: Our recent report (AASLD 2019) showed no significant difference in 1-year clinical relapse rate among overall 902 Nuc treated HBeAg negative CHB patients with consolidation duration of 1–2, 2–3 and ≥3 years. Comparing with ETV, TDF therapy is associated with much earlier off-therapy relapse. Whether consolidation duration required to be longer in this population remained unknown. Aim: To compare the optimal length of consolidation treatment in terms of 1-year clinical relapse (CR: HBV DNA ≥2000 IU/ml + ALT ≥2X ULN) rate between ETV and TDF treated patients.
Method: HBeAg negative CHB patients from two tertiary medical centres received ETV or TDF and had stopped therapy after demonstration of undetectable HBV DNA for more than 1 year with off-Nuc followed-up ≥1 year were recruited. The 1-year CR rate was compared among patients with consolidation therapy of 1–2 year vs. ≥2 years. Propensity score matching with age, cirrhotic status, prior treatment history, proportion of EOT HBsAg categorized level (≥200, 200–100, <100 IU/ml) at 1:1 ratio was performed to adjust the characteristics between off ETV and off TDF patients. Kaplan-Meir analysis and log rank test was performed to compare the consolidation duration impact on off ETV or TDF 1-year clinical relapse rate.
Results: A total of 428 patients were included, with 214 patients in each groups. Age, EOT age, gender, cirrhotic status, genotype, prior treatment history and proportion in EOT HBsAg ≥200, 100–200, <100 IU/ml were comparable between off ETV and TDF group. In Kaplan Meir analysis, the 1-year CR rate was significantly lower in off-TDF patients with consolidation ≥2 years than those <2 years (37.7% vs. 61.7%, log rank test, P = 0.001) whereas there was no difference (30.8% vs. 35.2%, log rank test, P = 0.400) in off-ETV patients.



Conclusion: The results have demonstrated that consolidation duration in off-TDF patients may require longer period ≥2 years to reduce the off-Nuc 1-year clinical relapse rate.

SAT457

Longer-term experience with tenofovir alafenamide (TAF) in HBV-infected patients; changes in EGFR, FIB4, ALT, and DNA suppression

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Background and Aims: TAF provides similar efficacy to tenofovir disoproxil fumarate (TDF) but with an improved safety profile particularly for bone loss and renal injury. However, continued benefit with longer-term TAF has not been sufficiently studied. Here we evaluate virologic suppression rates, eGFR, fibrosis, and ALT at 48+ weeks of TAF therapy in US clinical practice.
Method: TRIO has developed a national HBV network consisting of 6 academic and 4 community-based centers serving 17 US States to understand real-world HBV treatment. Of the 1037 patients enrolled from Jan 2017, 270 patients initiated TAF and remained on therapy for 48+ weeks as of Jan 2019. Lab measurement data at baseline and at or after (but nearest) 48 weeks of TAF therapy were collected. Elevated ALT was defined as >35 U/L for males and >25 U/L for females, HBV suppression was assigned for HBV DNA measures ≤2000 IU/ml. Comparisons between baseline and 48-week measures were made using McNemar's test (for dichotomous variables), Bowker's test (for multi-level variables) or t-test (for continuous variables). To identify variables associated with elevated ALT, eGFR <60 ml/min, or FIB4 >1.45 at 48 weeks, logistic regressions were conducted with adjustments for multicollinearity of variables.
Results: The study population (n = 270) was mostly male (59%), Asian (89%), and under or normal weight (60%) with a mean age of 53 years. Prior to initiating TAF, 81% of the patients received TDF, 8% entecavir, 6% were treatment naïve, 2% TDF/emtricitabine, 1% lamivudine, and 1% adefovir dipivoxil. As of Jan 2019, mean (median) TAF duration was 508 (512) days and ranged from 338 to 803 days. In paired analyses (Table), statistically significant changes were reduced mean ALT and increased DNA suppression; changes in FIB4 and eGFR were not significantly different between baseline and 48 weeks. Variables

associated with elevated ALT and eGFR <60 ml/min at 48 weeks were baseline elevated ALT (p < 0.001) and baseline eGFR <60 ml/min (p < 0.001), respectively. For FIB4 >1.45 at 48 weeks, significantly associated variables were baseline FIB4 >1.45 (p < 0.001) and Medicare as primary coverage (p = 0.010, collinear with Age ≥50).

Measures	Baseline (those on ≥48 weeks)	At 48 weeks	(% difference)	p
ALT, mean (SD) n	28 (26) n = 259	24 (13) n = 259	−15.1%	0.013
Normalized ALT, n (%)	201/259 (78%)	214/259 (83%)	6.5%	0.053
Suppressed HBV DNA, n (%)	247/256 (96%)	255/256 (100%)	3.2%	0.011
FIB4 >3.25, n (%)	13/237 (5%)	13/237 (5%)	0.0%	0.723
eGFR <60, n (%)	18/242 (7%)	21/242 (9%)	16.7%	0.366

Conclusion: This study of HBV-infected individuals receiving TAF for 48+ weeks found that statistically significant improvements occurred in ALT and HBV DNA suppression. Continued monitoring is ongoing to understand changes in these and other measures with longer term TAF.

SAT458

Immtav, a novel immunotherapy approach to eliminate hepatitis B virus

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Background and Aims: Treatment with nucleos(t)ide analogues, the current SOC for chronic HBV, effectively controls viral replication but does not sufficiently overcome immune exhaustion and whilst some agents in development are showing promise, they also require a long treatment duration. We have developed a potent bispecific molecule that redirects polyclonal T cells regardless of antigen specificity to eliminate HBV infected hepatocytes with the aim of delivering a rapid functional cure. ImmTAV molecules are bispecific fusion proteins, combining a high affinity TCR and an anti-CD3 (scFv) T cell activating moiety which are capable of specifically targeting HBV derived peptides presented by HLA on the surface of infected cells. The aim of this study was to demonstrate that ImmTAV molecules can potently, rapidly and specifically eliminate cells containing either integrated HBV DNA or those infected with HBV.
Method: Potency and specificity of ImmTAV molecules targeting the HBV envelope were tested against antigen positive (PLC/PRF/5 A2B2M, with integrated HBV DNA) and negative (HepG2 A2B2M) cell lines, as well as in a HepG2-NTCP *in vitro* infection system. Elimination of HBV envelope-positive cells was assessed using the Opera Phenix and the IncuCyte® Live cell systems, and the Primeflow RNA assay. Nucleos(t)ide analogues were added to the assay to look at the effect on T cell activation in the presence of ImmTAV molecules. T cells from peripheral blood of healthy donors were used as effectors in all experiments.
Results: In each of the formats tested, ImmTAV molecules mediated the specific elimination of cells containing integrated HBV DNA and the elimination of HBV-infected cells in an *in vitro* infection model (Figure), without killing antigen negative cells. The addition of nucleos(t)ide analogues to the assay did not change the potency of the ImmTAV.
Conclusion: ImmTAV molecules can potently and specifically eliminate HBV-infected cells, even in the presence of SOC nucleos (t)ide analogues. Our lead ImmTAV molecule IMC-I109 V has now gone through preclinical development to support first-in-human trials. These data provide evidence of a novel immunotherapeutic strategy that aims to achieve a rapid functional cure for people living with chronic HBV.

SAT459

HBV RNA decline without concomitant HBsAg decrease is associated with a low probability of sustained response and HBsAg loss

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Background and Aims: HBV RNA is a novel biomarker that may reflect intrahepatic HBV replication. Novel compounds have shown potent HBV RNA declines without concomitant HBsAg decrease. How this relates to long-term off-treatment response is yet unclear. We therefore aimed to study the degree of on-treatment HBsAg decline among patients with pronounced HBV RNA decrease in relation to off-treatment sustained response and HBsAg loss.
Method: We quantified HBV RNA (log copies/mL) and HBsAg (log IU/mL) in chronic hepatitis B patients who participated in two global randomized controlled trials (the 99–01 and PARC studies). In the 99-

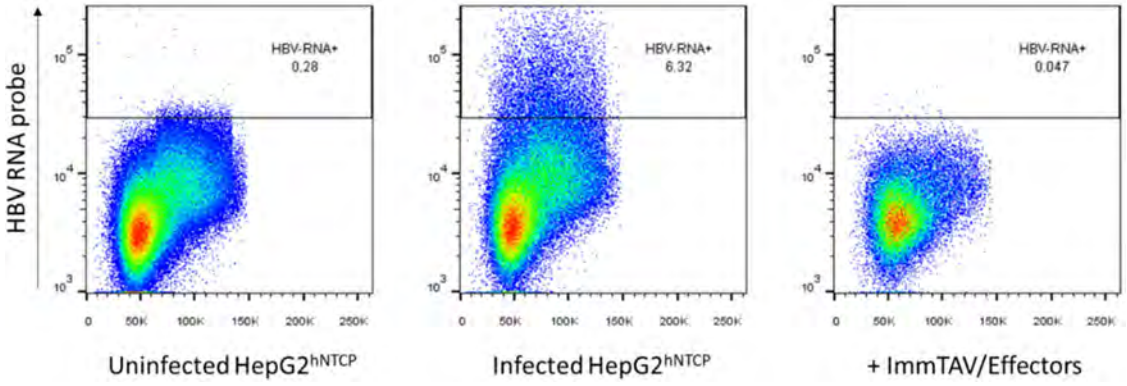

Figure: (abstract: SAT458): Elimination of HBV-infected cells by T cells when re-directed by HBV-specific ImmTAV.

01 study, HBeAg positive patients were randomized to peginterferon (PEG-IFN) ± lamivudine for one year; in the PARC study HBeAg negative patients were treated with PEG-IFN ± ribavirin for one year. Primary study endpoints were sustained response (SR), defined as HBV DNA < 2,000 IU/ml 6 months after end of treatment, and HBsAg loss.

Results: 279 patients were enrolled; 176 HBeAg positive, 103 HBeAg negative. SR was achieved in 57 (20.4%) patients and HBsAg loss in 18 (6.5%) patients. At week 24 of treatment, more pronounced HBV RNA decline was associated with higher rates of SR (13.6% with <1 log decline, 26.7% with >2 log decline) and HBsAg loss (1.2% with <1 log decline, 9.9% with >2 log decline; figure 1) at 6 months post-treatment. However, among 99 patients with at least 2 log HBV RNA decline at on-treatment week 24, 50 (50.5%) did not experience at least 0.5 log HBsAg decline at the same time point. Off-treatment sustained response rates were low in the absence of concomitant HBsAg decrease. Among patients with >2 log HBV RNA decline at week 24, SR was achieved in 15/34 (44.1%) of those with HBsAg decline >1 log, versus 8/50 (16.0%) patients without HBsAg decline (p < 0.001, figure 1). Similar observations were made for HBsAg loss; 10/34 (29.4%) with >1 log HBsAg decline at week 24, versus 0/50 (0.0%) in the absence of an HBsAg decline (p < 0.001, figure 1). Findings were consistent across other HBV RNA cut-offs, and at different time points (on-treatment week 12 and end-of-treatment).

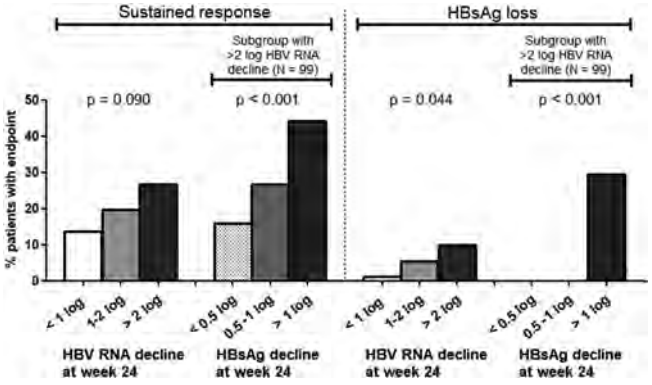

Figure 1: Rates of sustained response and HBsAg loss according to HBV RNA decline at week on-treatment 24, overall and stratified by HBsAg decline at week 24.

Conclusion: In this cohort, many patients with HBV RNA decline during PEG-IFN treatment did not experience HBsAg decrease. Absence of concomitant on-treatment HBsAg decline was associated with low rates of off-treatment sustained response and HBsAg loss. Future treatment trials should therefore consider kinetics of both biomarkers to adequately assess antiviral efficacy.

SAT460

HBV specific ImmTAV induce a broad immune response enabling the elimination of HBV positive cells

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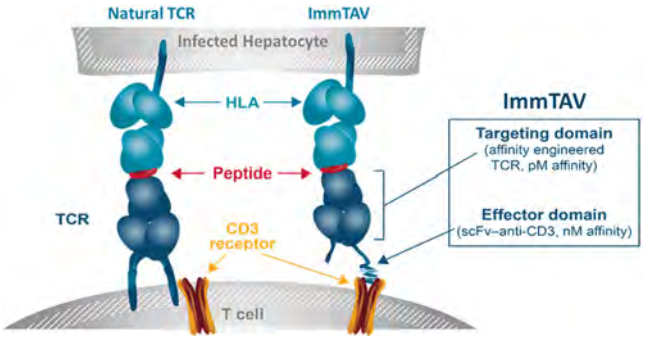
Background and Aims: It is widely acknowledged that an effective immune response is required to resolve chronic HBV. We have therefore, developed a potent bispecific molecule that redirects polyfunctional T cells regardless of antigen specificity to eliminate HBV infected hepatocytes with the aim of delivering a rapid functional cure. Current approaches show promise at blocking the viral lifecycle but the slow elimination of infected cells by hepatocyte turnover and exhausted virus specific T cells suggests that long treatment durations will be required to deliver a functional cure. The ImmTAX™ platform has the potential to dramatically accelerate the elimination of infected cells by engaging and redirecting non-HBV specific T cells. The potential of this approach is demonstrated clinically through tebentafusp, an ImmTAC® demonstrating single agent activity in metastatic melanoma. To test whether a HBV specific ImmTAV can redirect T cells and drive a polyclonal T cell response in a manner comparable to that of ImmTAC molecules (Figure 1), we examined the T cell subsets, cytokine and chemokine responses observed following *in vitro* exposure of HBV$^+$ cells to a HBV specific ImmTAV.

Method: Effector CD8$^+$, CD4$^+$, natural killer, MAIT and gamma delta T cells from healthy donor peripheral blood were isolated using magnetic bead separation or antibody-based cell sorting. ImmTAV mediated apoptosis of HBV$^+$ cell lines was measured with each subpopulation using Incucyte killing assays. Cytokine and chemokine release were measured over 5 days using the Luminex MagPix assay.

Results: Our data indicates that HBV specific ImmTAV molecules induce apoptosis of HBV$^+$ cell lines through redirection of multiple T cell subpopulations, including both CD8$^+$ and CD4$^+$ T cells. We show that each T cell subpopulation produces a broad range of cytokines and chemokines in response to ImmTAV-mediated stimulation. Detection of cell surface HLA presented HBV peptide by mass-spectrometry and quantification through binding of labelled TCR indicates that the commonly used cell line PLC/PRF/5 displays ~20 copies of antigen per cell, which is comparable to that required for tebentafusp mediated activity.



Conclusion: Preliminary results demonstrate that HBV specific ImmTAV molecules stimulate a broad cytokine and chemokine response, comparable to those observed clinically for tebentafusp, suggesting that ImmTAV molecules have the potential to accelerate elimination of infected HBV cells. This data supports the development of our lead HBV ImmTAV which has gone through preclinical development to support first-in-human trials.

SAT461

Safety and efficacy of tenofovir alafenamide in geriatric patients with chronic hepatitis B: experience from four ongoing phase 2 and phase 3 clinical trials

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Background and Aims: Recent studies demonstrate that the population with CHB is aging. Tenofovir alafenamide (TAF) is a first-line treatment for chronic hepatitis B virus infection (CHB), particularly in those at risk for TDF-associated bone and renal effects, including patients with advanced age. We reviewed our experience in the subset of geriatric CHB patients participating in ongoing TAF clinical trials.
Method: Included were patients age ≥65 y treated with TAF in 3 large Phase 3 trials (pooled analysis of viremic patients naïve to TAF in Studies 108 and 110, and suppressed patients switched from TDF to TAF [vs continued TDF] in Study 4018), and data from a single arm Phase 2 study in virally suppressed patients with renal and/or hepatic impairment switched to TAF from TDF and/or other antivirals (Study 4035). Efficacy (HBV DNA <29 or <20 IU/mL) and safety (adverse events [AEs], serious AEs, changes in hip and spine bone mineral density [BMD] and changes in creatinine clearance [$eGFR_{CG}$]) were

Table. TAF Efficacy and Safety in Geriatric vs Non-Geriatric CHB Patients

n/N (%)	TAF		TDF
	≥65 years	<65 years	≥65 years
Efficacy			
HBV DNA <20 IU/mL at Week 48			
Studies 108 and 110 (viremic)[a]	10/12 (83)	629/854 (74)	6/9 (67)
Study 4018 (TDF switch)	23/24 (96)	211/219 (96)	26/26 (100)
Study 4035 (renal impairment)[b]	46/47 (98)	45/46 (98)	NA
Study 4035 (hepatic impairment)[b]	6/6 (100)	25/25 (100)	NA
Renal and Bone Safety			
$eGFR_{CG}$ change at Week 48, mL/min, median (Q1, Q3)			
Studies 108/110 (viremic)	-3.6 (-9.0, +0.6)	-1.1 (-8.4, +7.7)	-10.2 (-12.0, -5.4)
Study 4018 (TDF switch)	+0.23 (-7.61, +4.08)	+1.04 (-4.46, +6.27)	-1.47 (-4.71, +0.60)
Study 4035 (renal impairment)[b,c]	-0.3 (-3.6, +3.6)	+0.9 (-4.2, +4.2)	NA
Study 4035 (hepatic switch)[b]	+1.6 (-2.4, +4.5)	+3.6 (-4.2, +10.2)	NA
Hip BMD % change at Week 48, median (Q1, Q3)			
Studies 108/110 (viremic)	-1.13 (-1.66, +4.18)	-0.20 (-1.53, +1.12)	-2.84 (-4.54, -1.42)
Study 4018 (TDF switch)	+0.84 (-0.64, +1.40)	+0.45(-0.40, +1.65)	-0.24 (-1.69, 0.21)
Study 4035 (renal impairment)[b]	+0.49 (-0.93, +1.36)	+0.39 (-0.92, +1.48)	NA
Study 4035 (hepatic impairment)[b]	+1.04 (-0.84, +1.48)	+0.61 (-0.77, +1.51)	NA
Spine BMD % change at Week 48, median (Q1, Q3)			
Studies 108/110 (viremic)	-2.13 (-5.50, -1.74)	-0.56 (-2.41, +1.17)	-4.34 (-5.53, -0.92)
Study 4018 (TDF switch)	+1.0 (-0.19, +2.60)	+1.60 (-0.17, +3.60)	-0.10 (-1.45, +1.25)
Study 4035 (renal impairment)[b]	+1.48 (-0.40, 3.16)	+1.21 (-1.25, +2.32)	NA
Study 4035 (hepatic impairment)[b]	+1.97 (+0.37, +3.36)	+1.53 (-0.18, +2.27)	NA

All efficacy results are missing=failure; bone and renal safety are observed data. $eGFR_{CG}$ is creatinine clearance (Cockcroft-Gault method). BMD is bone mineral density.
[a]For Studies 108/110 results are for HBV DNA <29 IU/mL. [b]Study 4035 results are at Week 24. [c]End-stage renal disease patients are not included in this analysis.

Figure: (abstract: SAT461)

assessed for older (≥65 y) vs younger (<65 y) patients. In Studies108, 110, and 4018, results for TDF in patients ≥65 y were also determined for comparison.
Results: A total of 124 patients ≥65 y were included, representing 6.5% of all enrolled patients. Other than age, decreases in renal/bone parameters, and increased comorbidities, the older and younger groups were generally similar. Efficacy and safety results are summarized in the Table. Rates of virologic suppression was comparable in geriatric vs non-geriatric patients treated with TAF. Overall, AEs and SAEs were similar between older vs younger patients; there were no Grade 3/4 AEs related to study drug in patients ≥65 y. Compared with younger patients, declines in $eGFR_{CG}$ and hip/spine BMD were greater in viremic older patients; however, the decreases were less than in older patients on TDF. In suppressed patients, $eGFR_{CG}$ increases were greater in younger vs older patients receiving TAF, while changes in hip and spine BMD were similar; TDF treatment resulted in declines in BMD and $eGFR_{CG}$.
Conclusion: The efficacy and safety of TAF in geriatric CHB patients were generally similar to younger patients. Small improvements in renal and bone parameters can be seen in older patients switched from TDF to TAF.

SAT462

Pharmacokinetics of VIR-2218, an RNAi therapeutic for the treatment of HBV infection, in healthy volunteers

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Background and Aims: VIR-2218 is an investigational N-acetylgalactosamine (GalNAc)-conjugated ribonucleic acid interference (RNAi) therapeutic in development for functional cure of chronic hepatitis B virus infection (CHB). VIR-2218 was created using Enhanced Stabilization Chemistry Plus (ESC+), which retains enhanced metabolic stability needed for in vivo potency while reducing sequence matched off-target effects. VIR-2218 is designed to silence all HBV transcripts, from both cccDNA and integrated DNA, across all 10 HBV genotypes. Preliminary pharmacokinetic (PK) data from the first-in-human Phase 1 randomized, blinded, placebo-controlled, dose ranging study of VIR-2218 in healthy volunteers are reported herein.
Method: Six single ascending dose cohorts of eight subjects (6:2 active:placebo) received a single subcutaneous (SC) dose of VIR-2218 ranging from 50 to 900 mg. Plasma samples were assessed to determine PK of VIR-2218 and active metabolite.
Results: VIR-2218 was absorbed after SC injection with median T_{max} of 4–8 hours. VIR-2218 was not measurable in plasma after 48 hours for any subject, consistent with rapid GalNAc-mediated liver uptake; the median apparent elimination half-life ($t_{1/2}$) ranged from 2.85–5.71 hours. Following single SC dose of 50 to 900 mg, plasma area under the curve (AUC_{last}) and mean-maximum concentrations (C_{max}) increased with dose with mean exposures ranging between 786 to 74,700 ng*hr/mL and 77.8 to 6010 ng/mL, respectively. Interpatient variability in VIR-2218 plasma PK parameters was generally low (~30%). In preclinical species, the most prevalent active metabolite (~12%), AS(N-1)3′ VIR-2218, is equally potent as parent VIR-2218. AS (N-1)3′ VIR-2218 was detectable in plasma in 0/6 subjects at 50 mg, 3/6 subjects at 100 mg and in all subjects at 200, 400, 600 and 900 mg. The PK profile of the metabolite was similar to VIR-2218 with AUC_{last} and C_{max} values of AS(N-1)3′ VIR-2218 in plasma ≤10% of VIR-2218.
Conclusion: VIR-2218 demonstrated favorable PK properties in healthy volunteers supportive of SC dosing and continued development. Evaluation of VIR-2218 in patients with HBV is ongoing.

SAT463

Characterization of IL-21-expressing recombinant hepatitis B virus (HBV) as a therapeutic agent targeting persisting HBV infection

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Background and Aims: Gene therapy based on adeno-associated virus (AAV) has been used for treatments in chronic hepatitis B virus (HBV) mouse model and achieved promising therapeutic effects. However, the nonspecific transduction of AAV and the integration of cargo gene into host genome could pose potential risks. Novel therapeutic vectors need to be developed. The hepatocyte tropism of HBV, as well as the accessibility of virions, makes HBV an ideal candidate for the development of hepatocyte-targeting therapeutic vector. We have generated a highly replicative HBV replicon plasmid, named 5c3c, with a maximized in-frame deletion within the functionally non-critical spacer region of polymerase, where cargo gene sequences can be inserted in-frame with the overlapping preS1-preS2-S open reading frame(ORF). Meanwhile, IL-21 has been reported to be positively associated with the outcome of HBV treatments in clinic and mouse models, which makes it a therapeutic gene for HBV.
Method: We cloned human or murine IL-21 gene into 5c3c to create recombinant HBV (rHBV) replicon (hIL-21-5c3c and mIL-21-5c3c, respectively). rHBV replicon plasmids were transfected into hepatoma Huh7 cells or injected into mice to collect rHBV virions. The infection and super-infection ability of virions was confirmed in HepG2 cells stably expressing NTCP (HepG2-NTCP) and human liver chimeric mice. Lastly, we assessed the anti-viral effects of rHBV replicon in chronic HBV mouse model.
Results: A large amount of rHBV virions carrying hIL-21 or mIL-21 could be obtained from in vitro and in vivo. These virions could infect HepG2-NTCP cells to initiate HBV gene expression (including IL-21) and replication. Most importantly, these virions possessed super-infection ability in both HepG2-NTCP cells and human liver chimeric mice. Lastly, we found rHBV replicon could clear HBV serum markers and intrahepatic HBV DNA (including rHBV DNA) with long-lasting HBV specific memory responses.

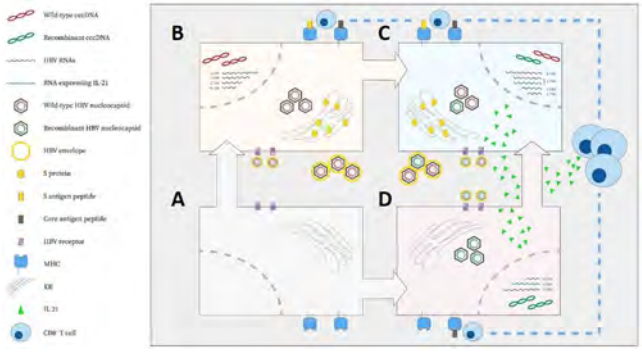

Figure: **Application of therapeutic rHBV virions to chronic hepatitis B treatments.** (A) HBV-free hepatocytes. (B) Wild-type HBV virions infect hepatocytes and then secretes progeny HBV. (C) rHBV virions super-infect hepatocytes. (D) rHBV virions infect HBV-free hepatocytes.

Conclusion: These results demonstrated rHBV virions carrying IL-21 gene could provide a novel vehicle for chronic HBV treatments.

SAT464

Optimising delivery of therapeutic hepatitis B vaccines to induce resident memory T cells in the liver

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Background and Aims: We have previously developed viral vectors (chimapanzee adenoviral [ChAdOx1] and modified vaccinia Ankara [MVA]) encoding hepatitis B virus (HBV) antigens for the therapy of chronic HBV infection. Used in heterologous prime-boost strategies, they generate high magnitude, polyfunctional T cell responses in mouse splenocytes. Since HBV is exclusively hepatotropic, the aim of this study was to evaluate the characteristics of vaccine induced intrahepatic T cells and target them to the liver by optimising vaccine delivery.
Method: C57BL6 mice were vaccinated with 5×10^7 infectious units (iu) ChAdOx1-HBV (prime, week 0) followed by 2×10^6 plaque forming units (pfu) MVA-HBV (boost, week 4). After intramuscular (i.m) ChAdOx1-HBV prime, MVA-HBV boost was delivered either i.m or intravenously (i.v) to assess its effect on intrahepatic T cell responses. Mice were sacrificed 14 or >60 days after MVA-HBV. Lymphocytes were isolated via mechanical dissociation and were surface stained using fluorochrome-labelled antibodies and a pentamer specific for the H2Kb restricted epitope VWLSVIWM. Cells were acquired on an LSRII flow cytometer (BD) and analysed by FlowJo v10 (BD). Statistical analysis was performed on PRISM v8 (GraphPad).
Results: Vaccine induced VWLSVIWM specific CD8 T cells in the blood and liver are predominantly CD44+CX3CR1+CD62L-. Liver T cells express higher CD69 (median fluorescence intensity [MFI] 13154 vs 2315, $p < 0.0001$) and CXCR6 (54.3% vs 16.1%, $p = 0.0008$) than in the blood at day 14 after boost vaccination. The magnitude of VWLSVIWM T cells is increased in the liver after i.v as compared to i.m MVA-HBV boost vaccination at day 14 (3.00% vs 4.90% of all CD8 T cells, $p = 0.04$) but not at >60 days after boost vaccination (3.11% vs 3.98%, $p > 0.05$).
Conclusion: Therapeutic HBV vaccination induces long lived T cells with a CD69+ tissue residency phenotype in the liver. Although the magnitude of vaccine induced T cells in the liver at day 14 after boost MVA-HBV vaccination can be increased by i.v rather than i.m administration, this was not sustained out to day 60. This transient increase of intrahepatic T cells after i.v. boost MVA vaccination may be sufficient to enable immunological control of HBV in chronic infection.

SAT466

Functional cure based on pegylated interferon ? in long-term nucleoside analog suppressed HBeAg negative chronic hepatitis B: a multicenter real-world study (Everest project in China), an interim report

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Background and Aims: HBsAg loss is regarded as functional cure and considered as an optimal treatment endpoint for chronic hepatitis B. In order to explore a better strategy to achieve functional cure and confirm the HBsAg loss rate of previous clinical studies in the real world, Chinese Foundation for Hepatitis Prevention and Control launched the multicenter real-world study that focused on functional cure, named Everest Project. (NCT04035837).
Method: The Everest Project plans to recruit 30,000 CHB patients from over 260 hospitals in China who had experienced effective NA therapy for more than one year, presented as HBV DNA<100 IU/ml, HBeAg negative and HBsAg<1500 IU/mL, between April 2018 and December 2021. Peg-IFNα "add-on" or "switch to" treatment for 48 to 96 weeks was selected by patients. The primary endpoints were HBsAg loss and seroconversion rates at 48 and 96 weeks.
Results: Up to now, 2673 eligible patients were recruited. 1427 patients who have completed 24 weeks of treatment and 516 patients who have completed 48 weeks of treatment were analyzed. 82.3%

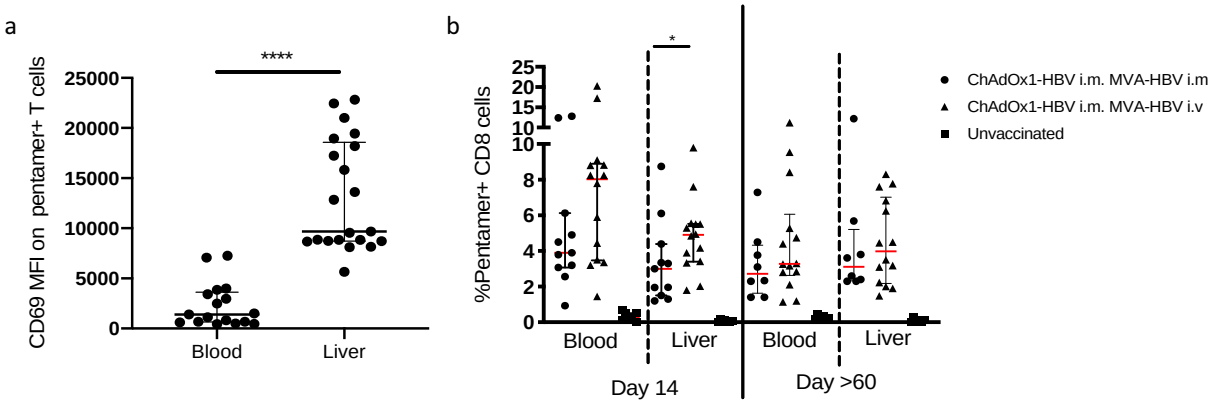

Figure: (abstract: SAT464): (a) MFI of CD69 in VWLSVIWM T cells (pentamer+) in the blood and liver and (b) percentage of VWLSVIWM T cells (pentamer +) in the blood and liver day 14 and day >60 after i.m or i.v MVA-HBV boost vaccination.

patients were male with a mean HBsAg baseline of 388.4 IU/ml. The overall rate of HBsAg loss for patients treated ≥12, ≥24, ≥36 and ≥48 weeks was 13.00%, 16.06%, 20.49% and 23.01%. Subgroup analysis based on baseline HBsAg stratification (0.05–100, 100–500, 500–1000, 1000–1500 IU/mL) found that the HBsAg loss rate was highest in patients with baseline HBsAg between 0.05 and 100 IU/mL (34.93% for patients treated ≥48 weeks).

Fig 1: Interim data of HBsAg loss of Everest Project in China. *The mean baseline of HBsAg was 388.4 IU/ml.

Conclusion: Functional cure can be well achieved in NA suppressed CHB patients by pegIFNα "add-on" or "switch to" strategies, especially for those with lower HBsAg baseline. Patients who complete the full course of treatment have the highest chance to functional cure. The rate of HBsAg loss in this large-scale real-world study is consistent with previous clinical research.

SAT467

Occurence of hepatocellular carcinoma in chronic hepatitis B patients undergoing entecavir or tenofovir treatment: a multicenter study in Taiwan

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Background and Aims: Nucleos(t)ide analogues (NUCs) treatment, including entecavir (ETV) or tenofovir (TDF), had been demonstrated to reduce the risk of hepatocellular carcinoma (HCC) development in patients with chronic hepatitis B (CHB). However, some studies reported an even lower risk of HCC occurrence by TDF as compared with ETV. We performed a multi-center study to compare the incidence of HCC between the two NUCs among lamivudine-naive CHB patients by collecting data from ten medical centers in Taiwan.
Method: From 2007, 5131 CHB patients had been received ETV or TDF treatment in this multicenter data cohort. Among them, 816 patients were excluded due to HCV coinfection, underlying HCC or malignancy, less than 6 months of treatment, lamivudine-experienced or resistance. Finally, 4315 patients were recruited in this study, including 3124 on ETV and 1191 on TDF treatment. Factors associated with HCC occurrence were evaluated.
Results: Of the 4315 patients, 1106 had underlying liver cirrhosis. As of the end of 2018, 192 patients developed HCC, with the incidence of 0.009 per person-year for ETV and 0.008 per person-year for TDF. Factors associated with HCC occurrence were age >55 y/o (HR = 2.717, 95% CI = 2.017–3.661, $p < 0.001$), male gender (HR = 1.441, 95% CI = 1.029–2.017, $p = 0.033$), and presence of cirrhosis (HR = 5.705, 95% CI = 4.162–7.821, $p < 0.001$) in multivariate analysis. There was no statistical difference in the risk of HCC occurrence between ETV or TDF treatment. In subgroup patients with cirrhosis, the incidence of HCC was 0.021 per person-year for ETV, and 0.025 per person-year for TDF. Again, TDF, as compared with ETV, did not further reduce the risk of HCC in univariate analysis. Only male gender and age >55 y/o were the significant factors related to HCC development in cirrhotic patients.
Conclusion: The statistical difference of the HCC risk between TDF and ETV was not reached in this multicenter, large cohort study, even in subgroup patients with liver cirrhosis.

SAT468

Anti-HBS induction and HBsAg reduction by nasal administration of a therapeutic vaccine containing HBsAg and HBcAg (NASVAC) in patients with chronic HBV infection

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Background and Aims: HBs antigen (HBsAg) loss is termed functional cure and recognized as an ideal treatment goal for the patients with chronic hepatitis B virus (HBV) infection. However, it is difficult to achieve functional cure by nucleos(t)ide analogs (NAs) or interferon. Thus NAs require long-term treatment. Further, chronic HBV infection without hepatitis, not recommended for anti-HBV therapy by current guidelines, needs suitable drugs for achieving functional cure, because these patients owe a risk for hepatic flare and hepatocellular carcinoma. This study was aimed to assess the efficacy of nasal administrative therapeutic vaccine, NASVAC, containing both HBsAg and HBcAg, on kinetics of HBsAg in CHB patient under NAs and chronic HBV infection without hepatitis.
Method: CHB patient with NAs and HBV carrier enrolled in an open-label clinical trial at Ehime University Hospital, Japan, after obtaining written consent and permission from institutional review board and enrollment of study to the clinical trial authority of Japan

(IRB#18EC003; registered to jRCT (#jRCTs061180100). NASVAC was emulsified in carboxyl vinyl polymer to increase the viscosity, then administrated for 10 times, once in every 2 weeks, by a special device designed for durable existence of NASVAC in nasal mucosa. Data were analyzed at 6 months after end of treatment (EOT).
Results: Twenty nine HBV patients under NAs treatment (NA group: age: 49–66 years, ALT: 16–28 U/L, HBsAg: 93–1942 IU/mL) and forty two chronic HBV infection without hepatitis (w/o NA group: age: 44–64 years, ALT: 16–29 U/L, HBsAg: 311–3706 IU/mL) were enrolled. 75% of NA and 74.3% of w/o NA displayed HBsAg reduction, the mean HBsAg reduction was 16.7% in NA and 18.3% in w/o NA at 6 months after EOT. 37.9% in NA and 58.5% in w/o NA developed anti-HBs. HBV-DNA reduction was observed in 68.2% of w/o NA and 3 patients showed sustained HBV-DNA negativity. 4 patients, two in NA and two in w/o NA, achieved functional cure.
Conclusion: NASVAC induced anti-HBs, and reduced HBsAg in CHB with NAs and chronic HBV infection. Overall 4 patients achieved functional cure by NASVAC. NASVAC could be a novel immune therapy for achieving functional cure in HBV infected patients.

SAT469
The development and application of a prognosis prediction model for children with chronic hepatitis B

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Background and Aims: Serum hepatitis B surface antigen quantification(qHBsAg) was considered to be a reliable marker to predict antiviral treatment outcome. However, whether qHBsAg could predict HBsAg seroclearance in children with chronic hepatitis B (CHB) remains unclear. The aim of the study was to develop a prognosis prediction model for children patients with CHB treated with interferon(IFN).
Method: 195 children patients aged 1–17 years with CHB were enrolled from January 2010 to February 2015 in 302 hospital, who were treated with IFN alpha 48 weeks, and the end of treatment following up at least 6 months. Lasso regression model was used for features selection. Multivariable logistic regression analysis was used to develop the predicting models. The performance of these models was assessed with respect to its calibration, discrimination, and clinical usefulness. Internal validation was assessed by internal validation cohort with 82 children patients with CHB, and data was gathered from March 2015 to October 2016. An independent validation cohort contained 111 consecutive children patients from January 2015 to March 2016 in 4 other hospitals.
Results: Predictors contained in two models: predictive model before treatment(the BT model) and predictive model after 12–24 weeks treatment(the AT model) included age, baseline qHBsAg, qHBsAg at week 24, the decreasing percentage of qHBsAg at week 24, HBeAg and CD4. The BT model showed good discrimination, with an AUC of 0.8415(AUC, 0.8340 and 0.8203 through internal validation and independent validation), and good calibration. The AT model showed good discrimination, with an AUC of 0.9038(AUC, 0.8816 and 0.8598 through internal validation and independent validation), and good calibration. Decision curve analysis demonstrated that two models were clinically useful. Analysis of key clinic features showed: at the end of 48 weeks IFN treatment, the incidence rates of HBsAg seroclearance was 54.05% (100/185) among the patients with under 4.88 years old. The incidence rates of HBsAg seroclearance was 82.76% (24/29) among the patients with qHBsAg ≤666.95 IU/ml before treatment. Among the patients with qHBsAg levels ≤386.05 IU/ml at week 24, incidence rates of HBsAg seroclearance was 84.55% (104/123). In addition, the decreasing percentage of qHBsAg was over 92.7% at week 24, the incidence rates of HBsAg seroclearance was 77.37% (106/137), which indicated that baseline HBsAg levels, or HBsAg levels at week 24 and the decreasing percentage of qHBsAg at week 24 were the strong predictors of HBsAg seroclearance. All of them are independent prognostic factors.
Conclusion: AT and BT models can be conveniently used to facilitate the individualized prediction of children with CHB before antiviral therapy, which were very important and clinically useful for prediction of HBsAg seroclearance in children with CHB treated with IFN.

Liver tumours: Therapy

SAT473
Pre-operative gamma-glutamyltransferase to lymphocyte ratio predicts long-term outcomes for intrahepatic cholangiocarcinoma following hepatic resection

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Background and Aims: Intrahepatic cholangiocarcinoma (ICC) is a heterogeneous hepatobiliary cancer with limited treatment options. A number of studies have illuminated the relationship between inflammation-based prognostic scores and outcomes in patients with ICC. However, reliable and personalized prognostic algorithm in ICC after resection is pending. To appraise the prognosis value of gamma-glutamyltransferase (GGT) to lymphocyte ratio (GLR) in ICC patients following curative resection.
Method: ICC patients following resection with curation intent (2009–2018) were divided into two cohorts: derivation cohort and validation cohort. The derivation cohort was used to explore an optimal cutoff value and the validation cohort was used to further evaluate the score. Overall survival (OS) and recurrence - free survival (RFS) were analyzed and predictors of OS and RFS were determined.
Results: 527 ICC patients were included and randomly divided into the derivation cohort (264 patients) and the validation cohort (263 patients). The two patient cohorts had comparable baseline characteristics. The optimal cutoff was 33.7. Kaplan-Meier curves showed worse OS and RFS in the GLR>33.7 group compared with GLR≤33.7 group in both cohorts. Univariate and multivariate analyses demonstrated GLR as an independent prognostic factor for OS (derivation cohort: hazard ratio (HR) = 1.457, 95% confidence interval (CI): 1.027–2.067, $P = 0.035$; validation cohort: HR = 1.562, 95%CI: 1.078–2.263, $P = 0.018$) and RFS (derivation cohort: HR = 1.465, 95%CI: 1.027–2.092, $P = 0.035$; validation cohort: HR = 1.564, 95%CI: 1.129–2.166, $P = 0.007$).
Conclusion: Preoperative GLR is an independent prognostic factor for ICC patients following curative resection. Higher GLR is associated with worse OS and RFS.

SAT474
LXR agonism potentiates sorafenib sensitivity in HCC by activating microRNA-378a transcription

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Background and Aims: Sorafenib is the first-line treatment for advanced hepatocellular carcinoma (HCC), but the clinical response to sorafenib is seriously limited by drug resistance. Dysregulation of

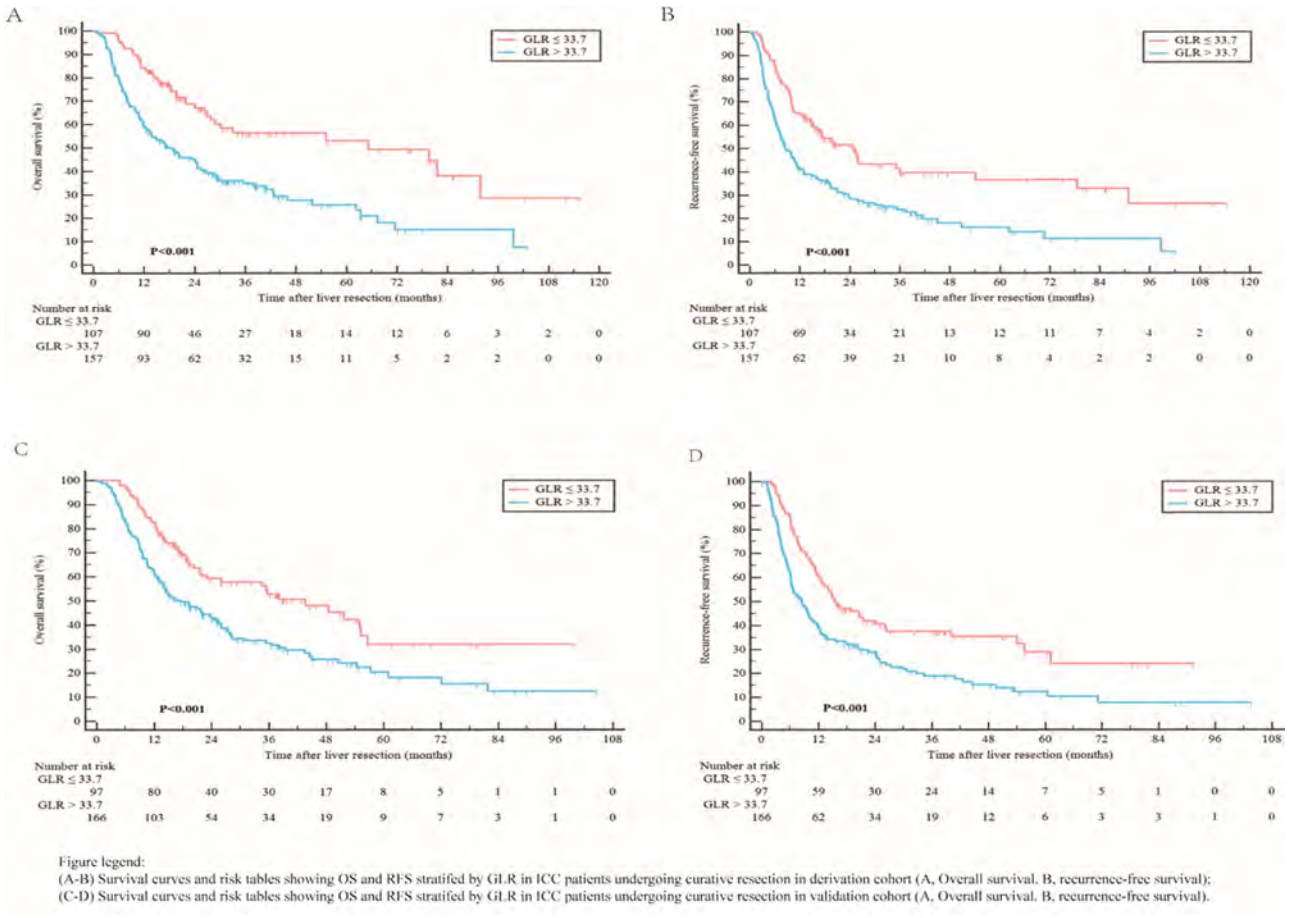

Figure legend:
(A-B) Survival curves and risk tables showing OS and RFS stratifed by GLR in ICC patients undergoing curative resection in derivation cohort (A, Overall survival. B, recurrence-free survival);
(C-D) Survival curves and risk tables showing OS and RFS stratifed by GLR in ICC patients undergoing curative resection in validation cohort (A, Overall survival. B, recurrence-free survival).

Figure: (abstract: SAT473)

microRNA play a critical roles in sorafenib resistance. Our studies have a better understanding of the dysfunction of microRNA in the sorafenib resistance and identify novel druggable targets for use in combination with sorafenib to increase its efficacy. in HCC cells.

Method: MicroRNA (miRNA) sequencing was performed to screen for potential miRNA candidates. Treatment with sorafenib resulted in sorafenib-resistant HCCs that were significantly depleted in miRNA-378a-3p, suggusting that miRNA-378a-3p play a crucial role in sorafenib resistance. We used RNA pulldown, western blots, immunohistochemistry, luciferase assays and immunoblotting to study the role of miR-378a in sorafenib resistance cell. To examine LXRa agonism in combination with sorafenib treatment, we added varying concentrations of sorafenib and LXRa agonist drugs to HCC cell lines. Patient-derived xenografts and cell-derived xenografts were used to study the functions of microRNA-378a and LXRa agonism.

Results: Our miRNA microarray data indicate that MicroRNAs (miRNA) were mostly downregulated in sorafenib resistance cell, such as microRNA-378a. There was a significant uncoupling of primer microRNA and pre-miRNAs levels in sorafenib-resistant cells. Down-regulation of xpo5 caused the precursor-microRNA-378 exporting nucleus limitation and restrained the maturation of microRNA, which reduced microRNA-378a expression conferring sorafenib resistance to hepatocellular carcinoma cells by activating IGF-1R to regulate RAS/RAF/ERK signaling pathways. LXRα (Liver X receptor alpha) functioned as a transcription activator of microRNA-378a and made sorafenib-resistance cells and model sensitive to sorafenib.

Conclusion: Attenuated XPO5-mediated export of precursor-miRNA limitation conferred sorafenib resistance in HCC. LXR agonist (GW3965) in combination with sorafenib represents a novel therapeutic strategy for HCC treatment.

SAT475

Ivermectin inhibits cholangiocarcinoma proliferation via induction of endoplasmic reticulum stress in vitro and vivo

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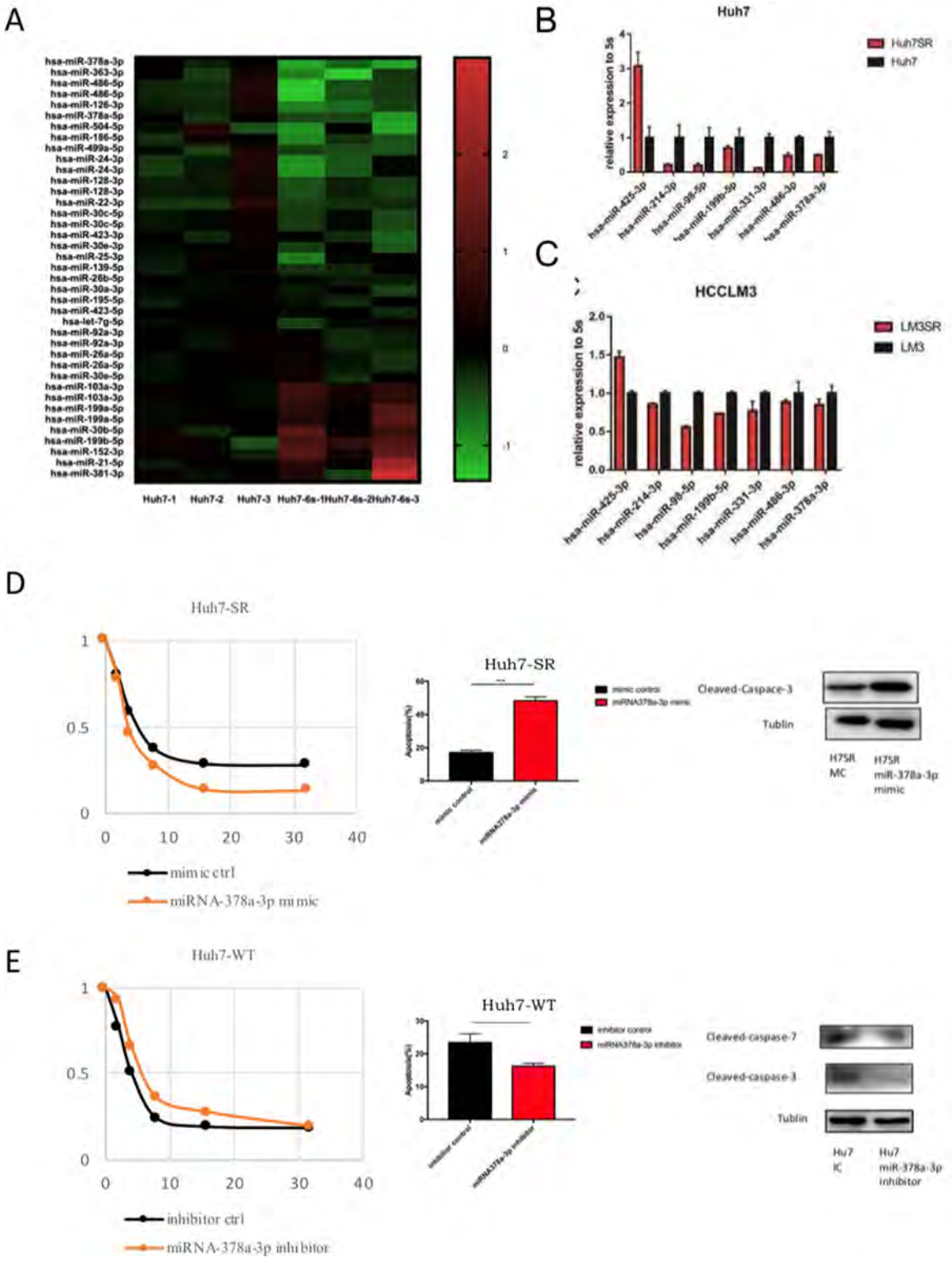
Background and Aims: Cholangiocarcinoma (CCA) is the second most common type of liver cancer, and is highly aggressive with very poor prognosis because of insensitivity to most of antitumor drugs. To reduce the mortality of cholangiocarcinoma and increase the possibility of cure, it is urgent and necessary to find effective and relatively safe drugs for the treatment of cholangiocarcinoma.

Method: In this study, we performed high-throughput drug screening, and found the river blindness drug Ivermectin (IVM) can inhibit Cholangiocarcinoma Proliferation in vitro and in vivo. RNA sequencing for ivermectin treated CCA cells prompted ER-Stress may play a vital role in inhibiting CCA cells proliferation. And thus, we studied the mechanism of induction of ER-Stress by ivermectin in CCA cell lines.

Results: Ivermectin inhibits CCA cell lines proliferation significantly via evaluating cell viability with Cell Counting Kit-8 after treated with 10 μM IVM dissolved with DMSO, while HIBEC cell (Human Intrahepatic Biliary Epithelial Cells) is not sensitive to IVM. The CCA cells treated with IVM are arrested in G1 phase. The results of colony formation assay demonstrate IVM can inhibit CCA cells proliferation.



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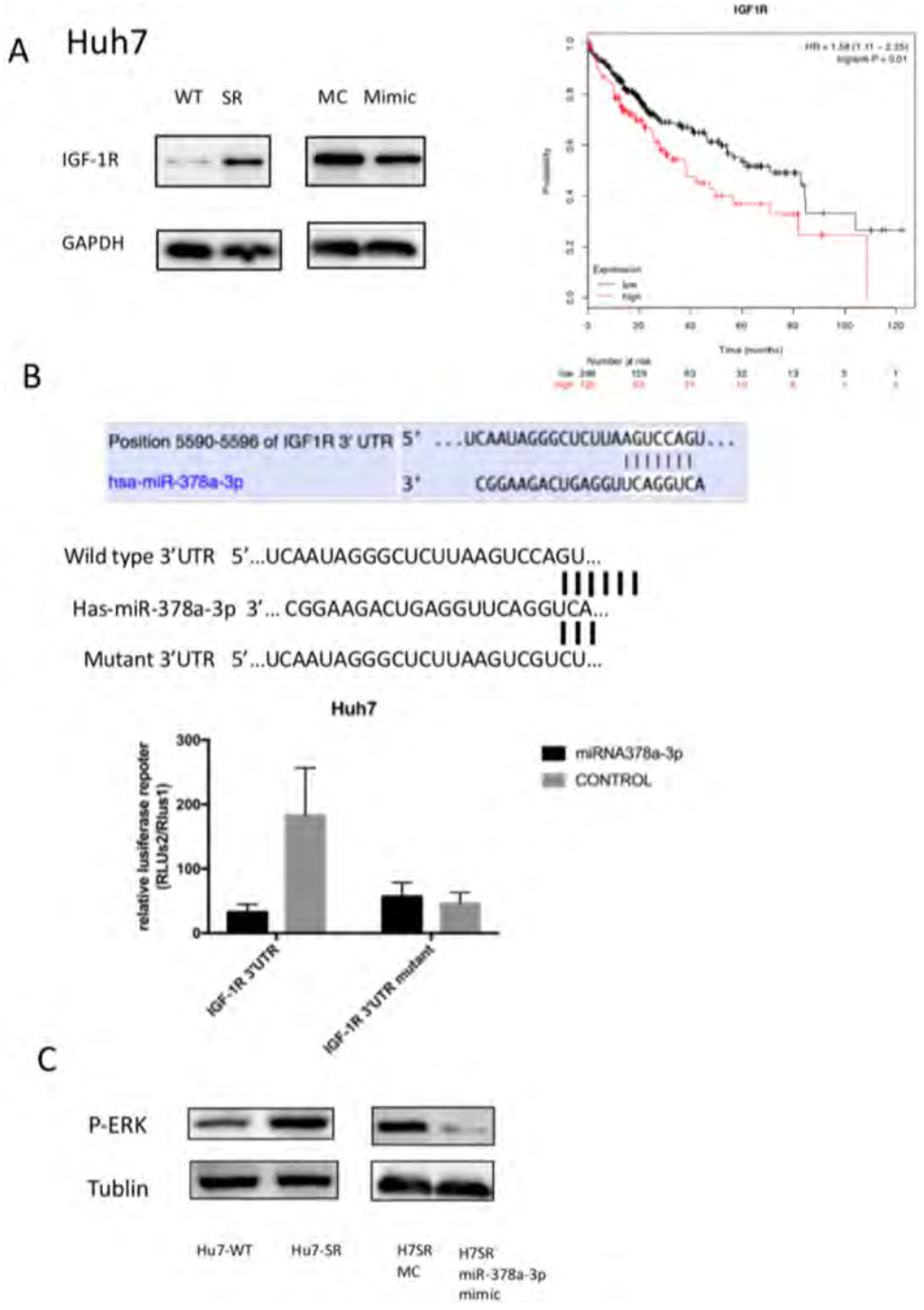

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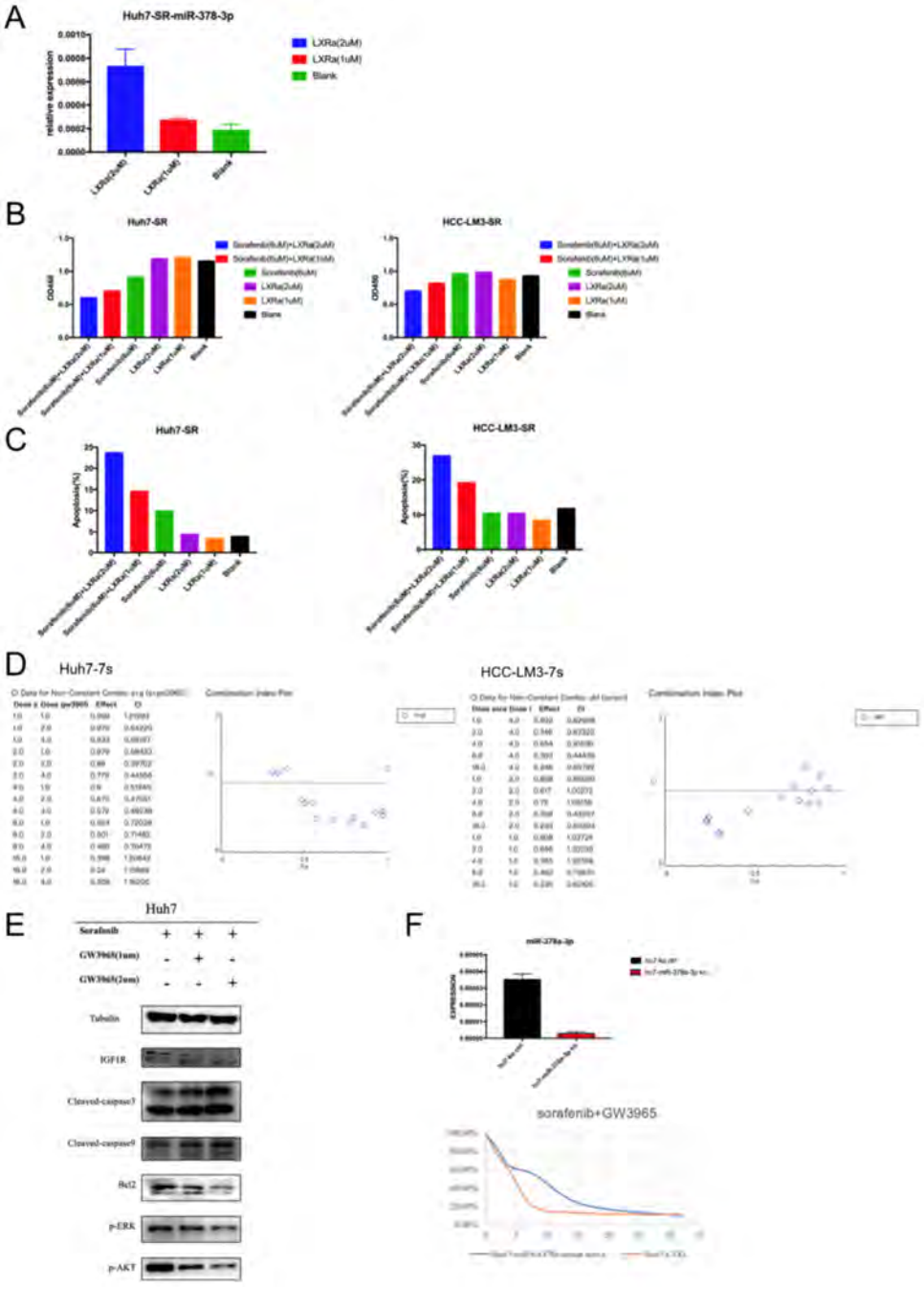

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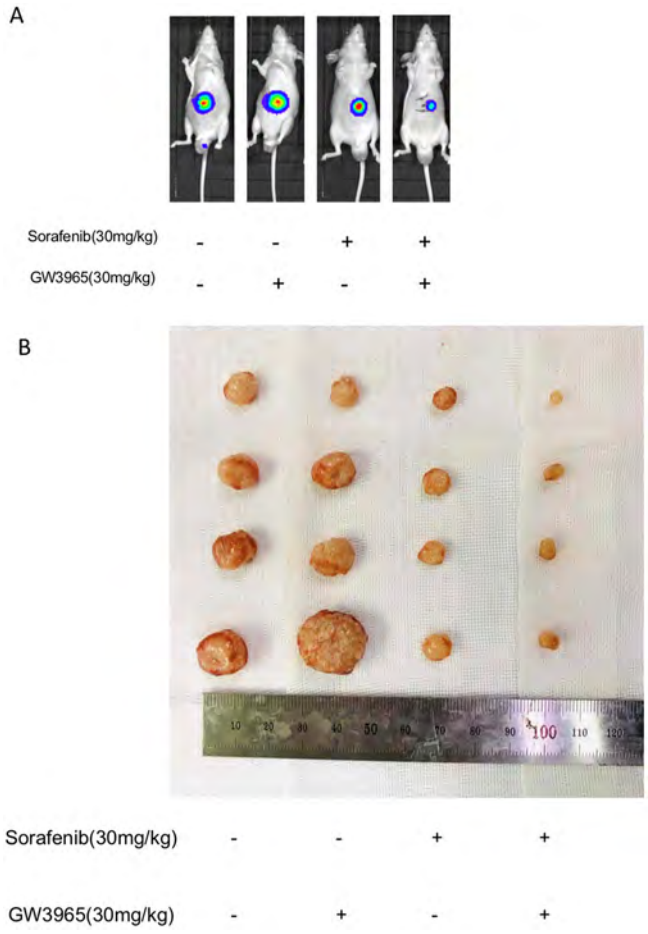

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Analysis of RNA sequencing to cells treated with IVM indicates induction of ER-Stress is potential mechanism of anti-tumor. Western-Blot experiments confirm ER-Stress play a vital role in this anti-tumor process. By constructing Patient-Derived tumor Xenograft (PDX) and Cell-Derived tumor Xenograft (CDX) subcutaneously in nude mice, IVM can inhibit CCA proliferation and have significant anti-tumor effect in vivo.
Conclusion: Ivermectin can inhibit cholangiocarcinoma cells proliferation in vivo and vitro via induction of ER-Stress and would be a promising drug therapy for cholangiocarcinoma, which provides novel treatment methods for CCA.

SAT476
Percutaneous microwave ablation versus open surgical resection for colorectal cancer liver metastasis

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Background and Aims: To compare the therapeutic outcomes between open surgical resection (OSR) and percutaneous microwave ablation (PMWA) for colorectal liver metastasis (CRLM) ≤3 cm.
Method: In this retrospective study, 200 consecutive patients with 306 CRLMs were reviewed. Overall survival (OS), disease-free survival (DFS), local tumour progression (LTP), intrahepatic distant recurrence, and extrahepatic metastasis were analysed to compare the therapeutic efficacy. Cox proportional hazards regression analysis was used to identify the prognostic factors for OS and DFS. Major complications and postoperative hospital stay were also assessed.
Results: The 1-, 3-, and 5-year OS rates were 91.6%, 64.1%, and 46.3%, respectively, in the PMWA group and 89.7%, 62.4% and 44.7%, respectively, in the OSR group (P = 0.839). The 1-, 3-, and 5-year DFS rates were 61.9%, 44.8%, and 41.3%, respectively, in the PMWA group and 58.1%, 24.4%, and 18.3%, respectively, in the OSR group (P = 0.066). The two groups had comparable 5-year cumulative rates of intrahepatic distant recurrence (P = 0.627) and extrahepatic metastasis (P = 0.884). The 5-year cumulative LTP rate was lower in the OSR group than in the PMWA group (P = 0.023). The rate of major complications was higher in the OSR group than in the PMWA group (P = 0.025), and the length of hospital stay after treatment was shorter in the PMWA group (P < 0.001).

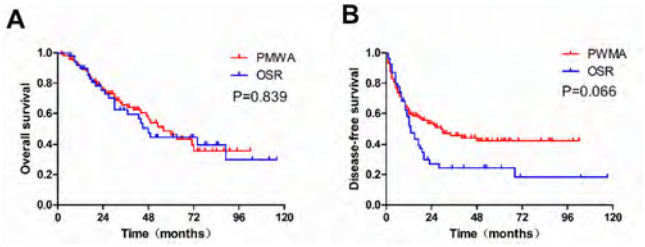

Figure: A: Graph shows cumulative overall survival rates after each treatment. The 1-, 3-, and 5-year overall survival rates were, respectively, 91.6%, 64.1%, and 46.3% in the PMWA group and 89.7%, 62.4%, and 44.7% in the OSR group. B: Graph shows cumulative disease-free survival rates after each treatment. The 1-, 3-, and 5-year disease survival rates of the PMWA group were, respectively, 61.9%, 44.8%, and 41.3% in the PMWA group and58.1%, 24.4%, and 18.3% in the OSR group. PMWA = percutaneous microwave ablation; OSR = open surgical resection.

Conclusion: There were no significant differences in OS or DFS between the two groups. PMWA was associated with increased LTP, fewer postoperative days and fewer major complications

SAT477
5-aminolevulinic acid mediated photodynamic therapy: pathing the way towards a new therapeutic modality for hepatocellular carcinoma

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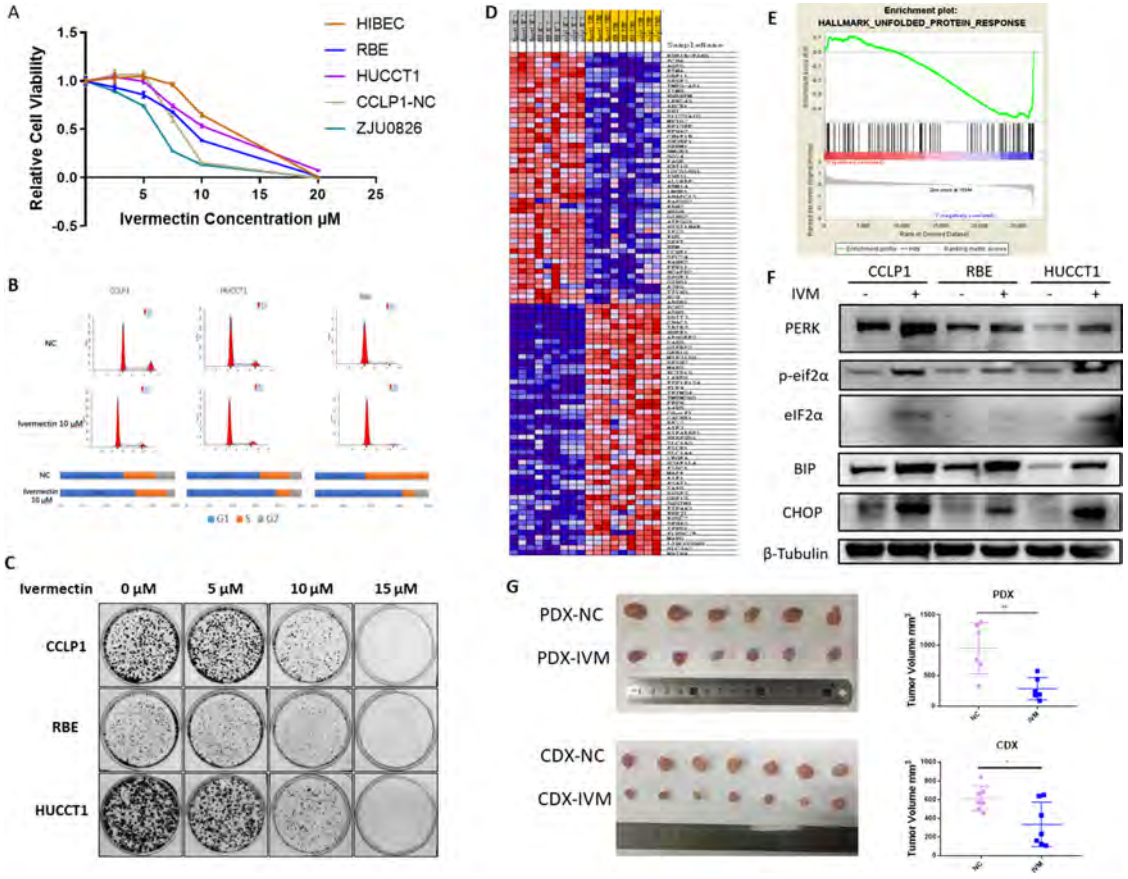
Background and Aims: Photodynamic Therapy (PDT) is a local anti-tumoral modality relying on systemic administration of a non-toxic dye, called Photosensitizer (PS), followed by illumination to elicit tumor cell death. Using 5-Aminolevulinic acid (5-ALA), the FDA-approved oral pro-drug of Protoporphyrin IX, the actual PS, we investigated the in-vitro impact of PDT over Hepatocellular Carcinoma (HCC) cell lines, and over healthy and tumoral liver cells obtained from surgical specimen of patients with HCC.



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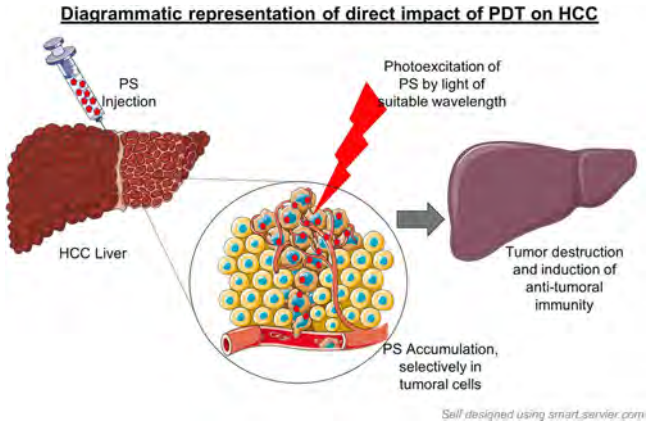

Method: Optimal 5-ALA PDT dosage was determined on three HCC cell lines; by testing different 5-ALA concentrations and illumination dosages. The efficacy was evaluated by analyzing viability, cellular proliferation and cytotoxicity, 24 hours post illumination. To examine safety of the therapy, primary healthy donor hepatocytes and liver myofibroblasts were treated by the optimal PDT dose, to measure their viability 24hr post illumination. Markers of fibrosis were analyzed by qPCR and ELISA, to observe fibroblast activation by 5-ALA PDT. To validate our findings, we investigated the viability of tumoral and healthy hepatocytes obtained from the same patient, till 12 days post illumination.

Results: In HCC cell lines, 5-ALA PDT induced a dose-dependent decrease of cellular viability; the optimal dose exhibiting IC50, thereafter, induced decreased cellular proliferation and increased cytotoxicity with respect to non-treated control. The viability of primary hepatocytes from a healthy donor treated with 5-ALA PDT decreased roughly 3 folds. Myofibroblasts treated by 5-ALA PDT did not exhibit any change in viability along with no change in mRNA expression levels of fibrosis markers. i.e. collagen-1, HSP47, αSMA, TIMP1, MMP2 together with no change in collagen secretion levels. When tested on tumoral and healthy hepatocytes from the same HCC patient, viability with respect to Non-Treated control decreased continuously up to 4 folds in both.

Conclusion: While having a negative effect on healthy hepatocytes, which might be due to the central role of the liver in heme-biosynthesis, the 5-ALA pathway for Protoporphyrin IX synthesis, our results still suggest that a non-targeted 5-ALA PDT can be effective to induce HCC cytotoxicity. Further studies are expected to develop targeted PS, which could localize selectively to the tumor core, along with surgical devices allowing targeted illumination of the tumor bedside intraoperatively, as an adjuvant to surgical resection.

SAT479

Transarterial radioembolization versus systemic treatment for the management of hepatocellular carcinoma with vascular invasion: analysis of the US national cancer database

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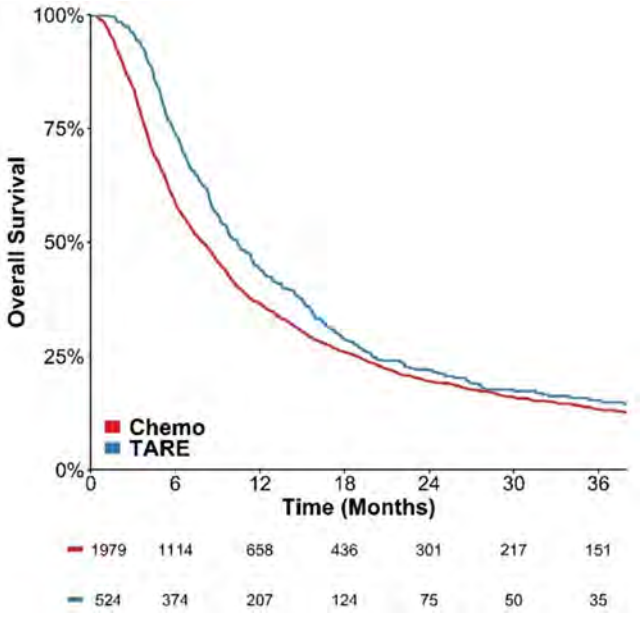
Background and Aims: For hepatocellular carcinoma (HCC) with vascular invasion, systemic treatment is recommended but transarterial radioembolization (TARE) is often used in clinical practice. The aim of this study was to investigate the outcome of patients who received TARE as a first-line treatment for HCC with vascular invasion in the United States (US).

Method: We performed a retrospective cohort analysis of the National Cancer Database (NCDB), which represents more than 70 percent of newly diagnosed cancer cases nationwide. All HCC patients diagnosed between 2010 and 2015 with the tumor stage of T3BN0M0 according to the 7th edition of the American Joint Committee on Cancer TNM staging system (tumor involving a major branch of a large vein of the liver without lymph nodes or extrahepatic metastasis) and received TARE or systemic treatment as a first-line treatment were included. Cox proportional hazard regression analysis was performed to identify factors associated with overall survival. Propensity score matching and inverse probability of treatment weighting adjusted analysis were performed to compare the outcome between TARE and systemic treatment.

Results: A total of 1979 patients who received systemic treatment and 524 patients who received TARE were included. The proportion of patients receiving TARE increased from 15.7% in 2010 to 31.4% in 2015. The median tumor size of the largest lesion was comparable (7.1 cm for systemic treatment vs. 7.0 cm for TARE, P = 0.43). In terms of overall survival, treatment at a community cancer program (hazard ratio [HR]: 1.43, 95% confidence interval [CI]: 1.12–1.82, p = 0.004) or comprehensive community cancer program (HR: 1.16, 95% CI: 1.03–1.29, p = 0.014) vs. academic cancer program, receiving care at the Midwest vs. Northeast region of the US (HR: 1.22, 95%: CI 1.06–1.41, p = 0.006), Charlson comorbidity index ≥3 vs. 0 (HR: 1.38, 95% CI 1.21–1.57, p < 0.001), larger tumor size (HR per cm: 1.04, 95% CI: 1.03–1.05, p < 0.001), elevated alpha-fetoprotein [AFP] vs. normal AFP (HR: 1.49, 95% CI 1.29–1.72, p < 0.001) were independently associated with shorter overall survival. With systemic treatment as a reference group, TARE was independently associated with improved overall survival (HR 0.80, 95% CI 0.72–90, p < 0.001).(Figure) Propensity score matching analysis (HR 0.81, 95% CI: 0.69–0.94, p < 0.001) and inversed proportion of treatment weight-adjusted analysis (HR 0.83, 95% CI: 0.78–0.89, p < 0.001) did not change the results.



Conclusion: Type and location of medical facilities, medical comorbidities, tumor size, elevated AFP, and type of HCC treatment were associated with overall survival in HCC patients with vascular invasion. Patients who received TARE had a longer survival compared to those who received systemic treatment. The role of TARE in combination with systemic treatment should be further investigated in HCC with vascular invasion.

SAT480

ALBI grade is a good predictive parameter for prognosis in advanced HCC patients with nivolumab therapy

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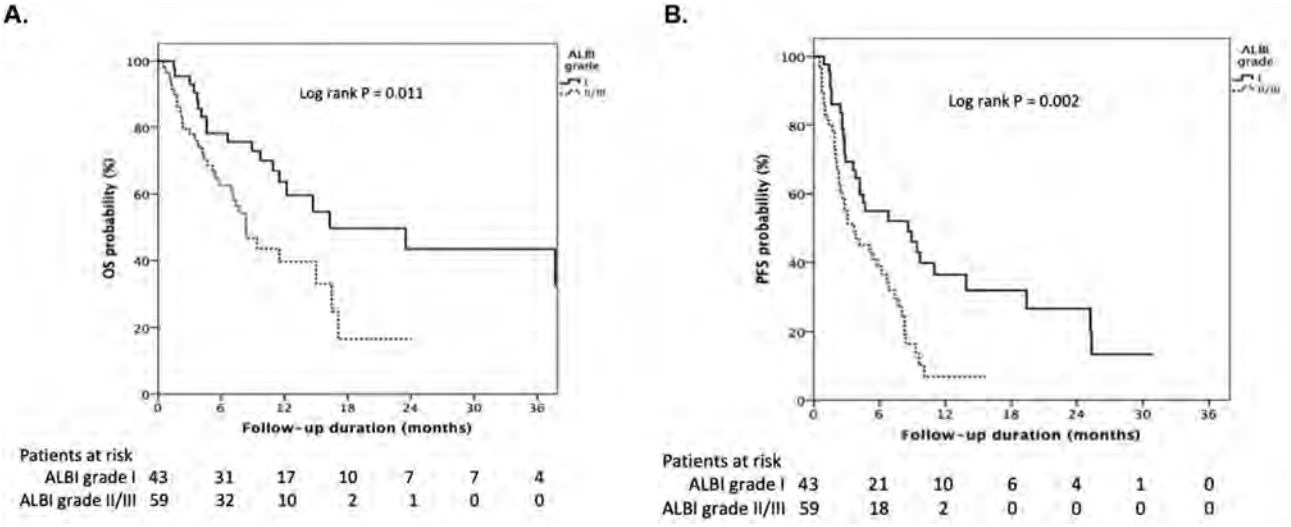
Background and Aims: The Albumin-Bilirubin (ALBI) grade is a new index for liver function evaluation using only albumin and total bilirubin level. This study aimed to investigate the application of ALBI grade after nivolumab therapy for prognosis prediction in advanced HCC patients.

Method: One hundred and eight patients who had advanced HCC experienced nivolumab were retrospectively reviewed between August 2015 and December 2018 in Chang Gung Memorial Hospital, Linkou Medical Center. Six patients were excluded due to Child-Pugh class C and a total of 102 patients were enrolled for analysis. Image response was reviewed by an independent radiologist according to RECIST v1.1. The Cox regression model was used to identify independent predictors of progression-free survival (PFS) and overall survival (OS).

Results: The median age was 61 (range 26–86) years old and most was male gender (78%). Chronic hepatitis B virus infection accounted for most etiology (67%) and 42% patients were ALBI grade I at baseline. Forty-two (41%) patients had no any systemic treatment experience before. Objective response after first course of nivolumab treatment occurred in 21% patients and 28 patients could occur best objective response during median follow-up duration 10.7 (range 3.5–49.1) months. The median PFS and OS were 4.7 and 12.2 months, respectively. By Cox regression analysis, AFP response (a >20% decline in serum AFP levels from baseline) at 12 weeks (aHR = 0.61, 95%CI = 0.34–0.97, P = 0.044), ALBI grade I (aHR = 0.48, 95%CI = 0.26–0.87, P = 0.015) and first objective response (aHR = 0.41, 95%CI = 0.17–0.97, P =



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0.043) were protective factors of OS while AFP response at 12 weeks (aHR = 0.38, 95%CI = 0.12–0.78, P = 0.043), ALBI grade I (aHR = 0.51, 95%CI = 0.28–0.94, P = 0.030) and AFP < 400 ng/ml (aHR = 0.37, 95%CI = 0.19–0.72, P = 0.003) were protective factors of PFS. Baseline ALBI grade I exhibited significantly longer OS (median 16.3 vs. 8.3 months, log rank P = 0.011) (Figure A) and PFS (median 8.6 vs. 3.7 months, log rank P = 0.002) (Figure B) compared with ALBI grade II/III.
Conclusion: ALBI grade was a good parameter to predict OS and PFS after nivolumab therapy in advanced HCC patients.

SAT481
Early changes in circulating FGF19 and ANG-2 levels as a possible predictive biomarker for lenvatinib therapy in hepatocellular carcinoma

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Background and Aims: Lenvatinib has become available as first-line therapy for patients with unresectable hepatocellular carcinoma (HCC). However, predictive biomarkers for the response to lenvatinib therapy have not yet been clarified. The aim of this study was to identify clinically significant biomarkers of lenvatinib therapy, to target strategies against HCC.
Method: Levels of circulating angiogenic factor (CAF) were analyzed in blood samples collected at baseline and at two, four, and eight weeks after introducing lenvatinib, from 74 Child-Pugh class A HCC patients who received lenvatinib. As CAF biomarkers, serum vascular endothelial growth factor (VEGF), fibroblast growth factor 19 (FGF19), FGF23, and angiopoietin-2 (Ang-2) were measured using enzyme-linked immunosorbent assays. The modified Response Evaluation Criteria in Solid Tumors were used to assess tumor response.
Results: When the analysis was stratified according to whether patients were lenvatinib responders (complete response or partial response) or non-responders (stable disease or progressive disease), significantly increased FGF19 levels (FGF19-i) and decreased Ang-2 (Ang-2-d) levels were seen on day 28 in lenvatinib responders as compared to non-responders (ratio of FGF19 level on day 28/baseline: responders vs. non-responders: 2.09 vs. 1.23, respectively, $P < 0.001$; ratio of Ang-2 level on day 28/baseline: 0.584 vs. 0.810, respectively, $P < 0.001$). Increases in FGF23 levels or VEGF on day 28 were not significantly different in responders versus non-responders. FGF19-i and Ang-2-d showed receiver-operating characteristic curve areas of 0.732 and 0.743, with specificity and sensitivity in discriminating responders from non-responders of 68.6% and 66.7%, respectively. In multivariate analysis, a combination of serum FGF19-i and Ang-2-d was the most independent predictive factor for lenvatinib response (HR, 8.283; 95%CI, 2.281–30.082; $P = 0.0013$). Progression-free survival (PFS) was significantly longer in the FGF19-i and Ang-2-d group (6-month PFS, 87.5%) than either the FGF19-i alone or Ang-2-d alone group (67.9%), or neither the FGF19-i nor low Ang-2-d group (33.0%, $P = 0.007$). Furthermore, the biomarker combination of serum FGF19-i and Ang-2-d showed the greatest independent association with PFS (HR, 0.298; 95%CI, 0.119–0.747; $P = 0.0098$) in multivariate analysis.
Conclusion: Early changes in circulating FGF19 and Ang-2 levels might be useful for predicting clinical response and PFS in HCC patients on lenvatinib therapy.

SAT482
The volume of enhancement of disease (VED) predicts the early response to treatment and overall survival in patients with advanced hepatocellular carcinoma treated with sorafenib

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Background and Aims: The response of patients with advanced HCC treated with sorafenib is still unpredictable. We analysed the predictive value of the Volume of Enhancement of Disease (VED), a new radiologic parameter based on the arterial enhancement coefficient (ΔArt%) in computed tomography, in the early evaluation of the response to sorafenib in patients with advanced HCC.

Method: We included patients with advanced hepatocellular carcinoma (HCC) who underwent a multiphase enhanced CT (multi-detector Somatom Sensation 64 CT scan) before (T0) and after 60–70 days of therapy with sorafenib (T1), enrolled between 2012–2016. The same target lesions utilised for the assessment of response were used for the calculation of size and for the calculation of VED (volume lesion × Δart%/volume lesion). We compared these values at T0 and T1 in patients with a clinical benefit (CB, the composite of complete response, partial response and stable disease) from therapy or with progressive disease (PD). Survival probability was evaluated in the study population and in the different subgroups of patients, based on tumor size and VED, but also on ancillary imaging findings and blood chemistries.
Results: Thirty-two patients with advanced HCC treated with sorafenib (25 men, 7 women, mean age 65.8 years) were selected. At T1 8 patients had CB (1 partial response, 7 stable disease) and 24 had PD. VEDT0 was >70% in 8/8 CB patients compared to only 12/24 patients in the PD group (P = 0.011). In CB patients, but not in PD, VEDT1 values were significantly lower than those at T0 (p = 0.018). No significant differences in the ancillary imaging findings were found between the two time points. Patients with VEDT0 >70% showed a significantly higher median survival than those with lower VEDT0 (506 vs. 266 days, p = 0.032). Patients with VEDT0 >70% and alpha-fetoproteinT0 ≤400 ng/ml had a significantly longer survival than all other combinations of the two biomarkers (median survival: 582 days vs. 208–213 days for the other combinations of the two biomarkers).
Conclusion: In patients with advanced HCC treated with sorafenib, VED is a novel and simple radiologic parameter obtained by contrast-enhanced CT, which could be helpful in selecting patients who are more likely to respond to sorafenib therapy, and with a longer survival. Patients with baseline VED value >70% and alpha-fetoprotein ≤ 400 ng/ml showed longer survival.

SAT483

Alcoholic liver disease is associated with a poorer survival after radioembolisation for hepatocellular carcinoma

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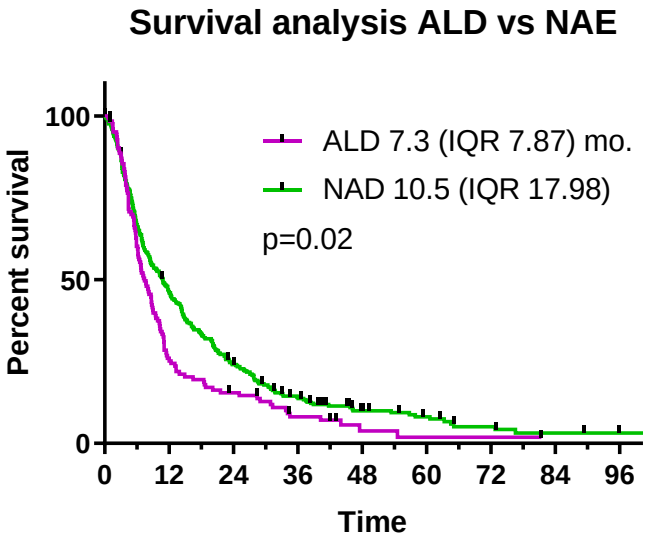
Background and Aims: Alcoholic liver disease (ALD) is a frequent predisposing risk factor for liver cirrhosis and hepatocellular carcinoma (HCC) in the Western World. Radioembolisation (RE) represents a safe and effective locoregional treatment option for advanced stage HCC in the absence of extrahepatic tumor burden. However, overall survival (OS) after RE shows heterogeneous outcomes, even within comparable BCLC stages. To address this, we aimed to identify independent risk factors that might be attributed to poorer OS after RE in a large monocenter cohort study.
Method: We performed a retrospective analysis of 453 patients with HCC who received RE between January 2006 and May 2014. ALD was defined as alcohol consumption of seven or more drinks weekly prior diagnosis of liver cirrhosis or HCC. Patients who did not fulfill these criteria were defined as non-alcoholic liver disease group (NAD). The main causes of HCC in the NAD group were 80 (24%) hepatitis C, 66 (20%) HBV infection and 97 (30%) NAFLD. All subjects were not amenable to surgical, systemic or alternative locoregional treatments and did not exhibit prognostically relevant extrahepatic metastasis.
Results: A total of 125 patients (27.6%) were diagnosed with ALD. Tumor burden and extension according to TNM classification and frequency of extrahepatic comorbidities did not differ between groups. Pretreatment with other modalities was more common in NAD (43 vs 26%; p < 0.01). ALD patients showed an inferior performance status due to hepatic morbidity (p < 0.01). Advanced liver disease was more common in ALD and an inferior Child Pugh and BCLC stage was evident (p < 0,05). However, toxicity determined by ALBI Score did not differ between the two groups (p = 0.42). Of note, ALD showed an inferior median overall survival 7.3 (IQR 7.87) months vs 10.5 (IQR 17.98) p < 0.02. However, after stratification for BCLC stage no difference was evident (Stage A p = 0.82, Stage B p = 0.22, Stage C p = 0.11).



Conclusion: ALD patients had a poorer overall survival in this large single center cohort. Therefore, we postulate, that history of alcohol abuse should be considered as relevant risk factor in the evaluation process for RE.

SAT484

HBsAg relapse after living donor liver transplantation in hepatocelluler carcinoma patients with hepatitis D virus infection may result in hepatocellular carcinoma relapse

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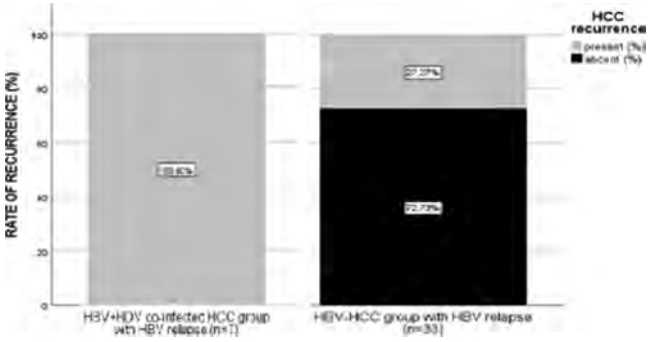
Background and Aims: Most frequent etiology of hepatocellular carcinoma (HCC) is viral hepatitis related liver cirrhosis. In the present study, we aimed to evaluate HCC recurrence following living donor liver transplantation (LDLT) patterns in patients with HBV and HDV infection.
Method: HBV related (n = 163 [84%]) or HBV+HDV co-infected (n = 31, [16%]) HCC that received LDLT were included in the study. Demographic data, Milan criteria, disease free survival (DFS), HCC and HBV recurrence was evaluated. The first year following the liver transplantation monthly routine laboratory evaluation including liver function tests, complete blood count and alpha-feto protein (AFP) together with abdominal ultrasound (USG) were performed.

Abdominal computerized tomography (CT) or magnetic resonance imaging (MRI) was obtained every three months for the first year. Postoperative Hepatitis B recurrence was considered as hepatitis B surface antigen positivity determined after the postoperative third month.

Results: The median age of the patients was 55 (23–72) years. The two groups were similar in terms of demographic characteristics except body mass index was lower in HBV+HDV co-infected HCC group ($p < 0.05$). There was no statistically significant difference among the study groups in terms of tumor recurrence ($p > 0.05$). HBV +HDV co-infection significantly increased the HCC recurrence rates of the patients with tumors beyond the Milan criteria ($p < 0.05$). DFS was similar among the both groups ($p > 0.05$). HBV recurrence in HBV +HDV co-infected individuals showed 100% HCC recurrence ($p < 0.05$).



Conclusion: HDV enhances the tumor progression and causes recurrence in tumors beyond the Milan criteria following LDLT. Additionally, HBsAg relapse after LDLT with HBV and HBV+HDV co-infection means HCC relapse. In HBV+HDV co-infected HCC group HCC recurrence ocurred 100% if the patients have HBV recurrence. HBV recurrence in the postoperative period seems to be risk factor for HCC recurrence in both HBV-HCC and HBV+HDV co-infected HCC groups. So we made some changes regarding our approach to patients with HDV related HCC cases which includes a more strict surveillance program regarding the antiviral therapy and increased HBIg doses in our protocol.

SAT485

13C-methacetine breath test for the prediction of liver damage caused by transarterial chemoembolization in patients with hepatocellular carcinoma

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Background and Aims: Transarterial chemoembolization (TACE) can lead to deterioration of liver function during the treatment of hepatocellular carcinoma. The LiMAx (maximum liver function capacity test) is a real-time breath test for liver function capacity. The aim of our study was to investigate the relationship between hepatic side effects of a TACE and the LiMAx result.

Method: 70 patients (55 male, 66 with liver cirrhosis) with HCC and planned TACE were prospectively included in the study. In all patients, a LiMAx test was performed 0–7 days before TACE. Before TACE, the average body mass index was 30+/−6 (22–42) and the MELD score 10 ± 3 (6–18) points. The Child-Pugh-Score (CPS) was A in 60 and B in 10 patients. Side effects (NW) after TACE were recorded according to CTCAE classification. LiMAx values as well as classical parameters of liver function were compared with the occurrence of NW.

Results: Within 4 weeks after TACE, 30/70 patients had reported side effects including 7 patients with side effects grade II-III. Severe side effects included development or worsening of ascites in 6 and hepatic encephalopathy in 1 patient. In 5 patients there was an increase in the CPS score resulting in 5 patients switching from Child A to B, whereas no patient changed to CPS C. Side effects >grade II occurred only in patients with LiMAx value of 250 before TACE. Patients with CPS A before TACE which experienced severe side effects had initially LiMAX test results >180. The LiMAx test (AUC = 0.83) allowed a stronger prediction for the occurrence of side effects compared to albumin (AUC = 0.38), CPS (AUC = 0.68), ALT (AUC = 0.62), MELD score (AUC = 0.71) or bilirubin (AUC = 0.69) in the ROC curve analysis.

Conclusion: Measuring liver function using a 13C methacetine breath test is a helpful method for early identification of patients at risk of liver function deterioration by TACE.

SAT486

Influence of acute kidney injury on the prognosis of patients receiving transarterial transembolisation for hepatocellular carcinoma: based on ICA-AKI criteria

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Background and aim: Hepatocellular carcinoma (HCC) commonly develops in patients with liver cirrhosis. Acute kidney injury (AKI) is an independent prognostic factor for overall survival in patients with cirrhosis. In recent years, the new AKI criterion (International Club of Ascites, ICA-AKI) has been introduced in patients with cirrhosis to assess the early change of renal function and classify the status of AKI. This study aimed to investigate the influence of AKI on the prognosis of HCC patients receiving transarterial chemoembolisation (TACE).

Method: A total of 347 HCC patients with Child-Pugh class A and pre-TACE serum creatinine (SCr) ≤1.5 mg/dL receiving TACE as an initial therapy between 2000 and 2014 were analyzed. Overall survival with related risk factors in patients with HCC underwent TACE including AKI was investigated. We assessed AKI using SCr at 2 days, 2 months, and 4 months after TACE. The AKI stage after TACE is defined considering ICA-AKI criteria: stage 0, no increase of SCr or an increase of SCr <0.3 mg/dl; stage 1, an increase of SCr≥0.3 mg/dl or SCr≥1.5–2 times from baseline; stage 2, an increase of SCr≥2- 3 times from baseline; stage 3, an increase of SCr≥3times from baseline, or SCr≥4.0 mg/dl with an acute increase of ≥0.3 mg/dl, or an initiation of renal replacement therapy.

Results: The mean age was 60.9 years. Of 347 patients, death was observed in 109 patients (31%) and the median time of overall survival was 81 months. The mean SCr levels at pre-TACE, 2 days, 2 months, and 4 months after TACE were 0.9, 0.9, 0.9, and 1.1 mg/dL, respectively. The AKI within 4 months after TACE developed in 37 patients (11%). The AKI stages were stage 0 in 310 (89%), stage 1 in 10 (3%), stage 2 in 10 (3%), and stage 3 in 17 patients (5%). The multivariable analysis demonstrated that the risk factors for overall survival were serum albumin ≤3.5 g/dL (hazard ratio [HR] 1.56, $p = 0.031$), pre-TACE alpha-fetoprotein ≥100 ng/mL (HR 1.60, $p = 0.023$), BCLC stage B or C (HR 2.73, $p < 0.001$), bilobar location of HCC (HR 1.86, $p = 0.005$), AKI stage 1 (HR 7.45, $p < 0.001$), AKI stage 2 (HR 7.61, $p < 0.001$), and AKI stage 3 (HR 17.10, $p < 0.001$).

Conclusion: AKI is an independent prognostic factor for overall survival in patients receiving TACE for HCC. The AKI and its stage based on ICA-AKI criteria may be helpful to evaluate the prognosis of HCC patients treated with TACE.

SAT487

Radiofrequency versus microwave ablation for hepatocellular carcinoma within the Milan criteria in challenging locations: a retrospective controlled study

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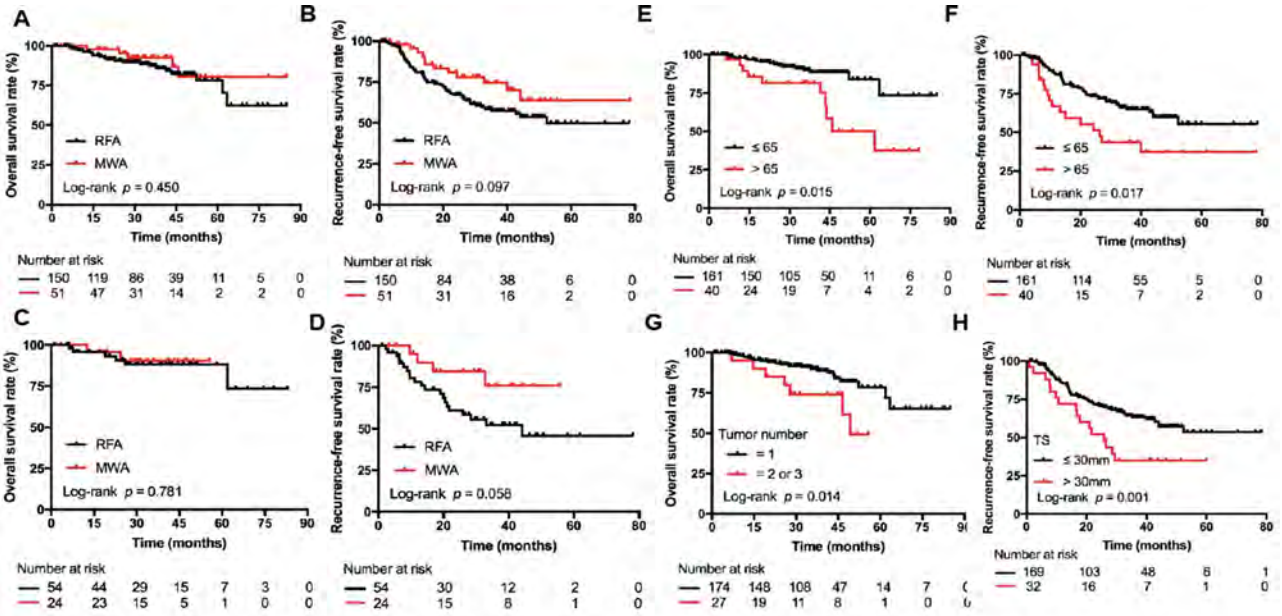
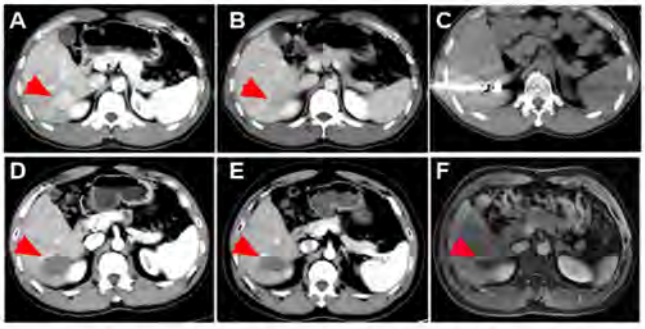
Background and Aims: As local ablation therapies, radiofrequency ablation (RFA) and microwave ablation (MWA) are two most often performed procedures for treatment of patients with hepatocellular carcinoma (HCC). The anatomical location of liver tumor has been validated as a significant prognostic factor associating with local efficacy and treatment-related complication after percutaneous thermal ablation. The purpose of this study was to compare the safety and efficacy of RFA with those of MWA for patients with the Milan criteria HCC in challenging locations.

Method: We retrospectively investigated 201 consecutive patients with the Milan criteria HCCs who underwent RFA (RFA group, n = 150) or MWA (MWA group, n = 51) between January 2012 and December 2016. Overall survival (OS), recurrence-free survival (RFS), local tumor control, and complications related to the treatments were compared between the two groups. Prognostic factors were analyzed by the Cox proportional hazard regression model.

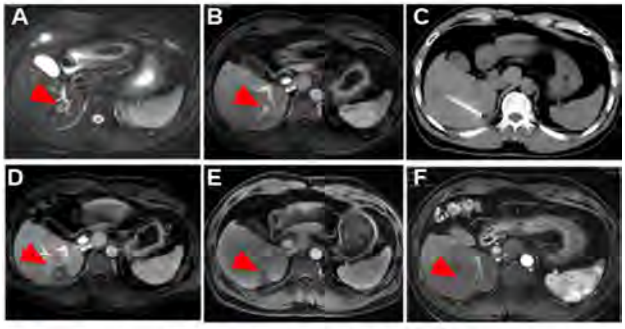
Results: Median follow-up duration was 36.7 months (range: 6.2–64.0 months). Cumulative 1-, 3-, and 5-year OS rates were 97.9%, 92.3%, and 80.6% in the MWA group and 96.4%, 87.4%, and 78.2% in the RFA group, respectively (P = 0.450). Cumulative RFS rates at 1, 3, and 5 years were 93.2%, 74.4%, and 63.7% in the MWA group and 80.3%, 57.3%, and 49.6% in the RFA group, respectively (P = 0.097). Multivariate analyses showed that patient age above 65 years (P = 0.004) and tumor number more one (P = 0.004) were associated with overall mortality, and patient age above 65 years (P = 0.048) and tumor size greater than 3 cm (P = 0.009) were associated with inferior RFS. The incidences of major complications were not significantly different between the two 46 groups (3.3% vs 3.9%, P = 0.843).



Kaplan-Meier curves of overall survival (A) and recurrence-free survival (B) in all 201 patients with the Milan criteria HCCs after RF A and MWA.
Kaplan-Meier curves of overall survival (C) and recurrence-free survival (D) in patients with subcapsular HCCs after RF A and MWA.
Kaplan-Meier curves of overall survival (E) and recurrence-free survival (F) in patients with an age of above 65 years.
Kaplan-Meier curves of overall survival (G) in patients with a tumor number of more than 1 and recurrence-free survival (H) in patients with an age of above 65 years.



Representative pictures of patient with the Milan criteria HCC in challenging location after RFA. A&B: Pre-RFA CT images (A: arterial-phase CT; B: portal-phase CT; the red arrow shows the location of HCC); C: A plain CT scan during the RFA procedure shows the well location of RFA electrode probe; D-E: Post-RFA arterial-phase CT images at 3-month (D) and 1-year (E); F: Post-RFA contrast-enhanced T1WI image at 5-year.



Representative pictures of patient with the Milan criteria HCC in challenging location after MWA. A&B: Pre-MWA MRI images (A: contrast-enhanced T1WI; B:T2WI; the red arrows show the location of HCC); C: A plain CT scan during the MWA procedure shows the well location of MWA electrode probe; D-G: Post-MWA MRI images (contrast-enhanced T1WI) at 3-month (D), 1-year (E) and 5-year (F), respectively.

Figure: (abstract: SAT487)

Conclusion: For patients with the Milan criteria HCCs in challenging locations, RFA and MWA were both safe and effective treatments that appeared comparable safety, local tumor control, and long-term survival.

SAT488

Effectiveness of sorafenib dose modifications on treatment outcome of hepatocellular carcinoma: analysis in real-life settings

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Background and Aims: Controlling adverse events through dose reduction can enhance drug adherence and treatment response. Currently, there is no guide for sorafenib dosing. The aim of this multicenter, retrospective, real-life, cohort study was to evaluate whether sorafenib dosing could affect treatment outcomes.
Method: A total of 782 hepatocellular carcinoma (HCC) patients treated with sorafenib between 2008 and 2018 were evaluated for sorafenib dosing and its modifications via medical records at baseline and regular followed-up. Study outcomes included progression-free survival (PFS), overall survival (OS), sorafenib duration, cumulative dose, adverse events (AEs), and drug discontinuation.
Results: The median patient survival was 5.2 months. Overall, 242 (30.9%) patients underwent dose reduction and 121 (17.5%) discontinued sorafenib due to AEs. In multivariate analysis, dose reduction was identified to be independently predictive of PFS and OS. Dose reduction from 800-to-400 mg/d provided significantly better PFS than dose maintained at 800 mg/d or dose reduction from 800-to-600 mg/d. Likewise, dose reduction from 800-to-400 mg/d resulted in a significantly better OS than other dosing. However, dose reduction to 200 mg/d led to significantly worse PFS and OS. Hand-foot skin reaction and drug discontinuation due to AEs were higher in the 800-to-600 mg/d group than 800-to-400 mg/d group. The 800-to-400 mg/d group had significantly longer treatment duration and higher cumulative dose than the 800 mg/d-maintained group.
Conclusion: Sorafenib dose reduction can improve HCC survival and increase patient tolerance and adherence coupled with longer duration and higher cumulative dose. Dose reduction from 800 mg/d to 400 mg/d than to 600 mg/d is recommended when clinically warranted. However, dose reduction to 200 mg/d is not recommended.

SAT490

Mutations in circulating tumor DNA predict primary resistance to systemic therapies in patients with advanced hepatocellular carcinoma

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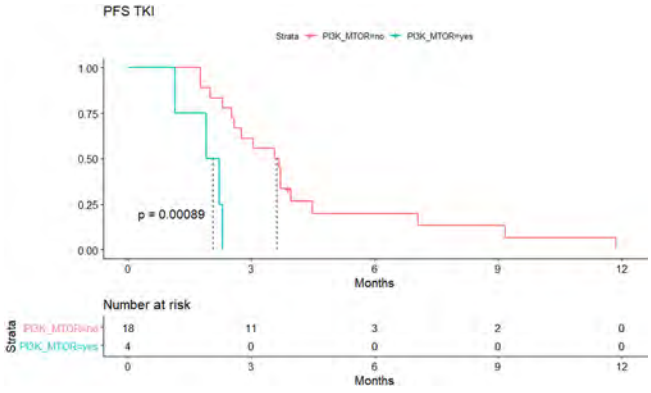
Background and Aims: Despite our understanding of the key molecular alterations of early stage hepatocellular carcinoma (HCC), little is known about the mutational landscape of advanced HCC. Predictive biomarkers of response to systemic treatment are also lacking. Mutations detected in HCC tissue affecting the WNT/b-catenin and PI3 K pathways have been associated to primary resistance to immune checkpoint blockade (CPI) and tyrosine kinase inhibitors (TKI), respectively(Harding et al. Clinical Cancer Res. 2019). We aimed at describing the mutational landscape of advanced HCC and identifying predictors of primary resistance to CPI or TKI using liquid biopsy, specifically circulating tumor DNA (ctDNA).
Method: We prospectively enrolled patients with HCC at advanced stages receiving systemic therapies between October 2015 and January 2019. We conducted mutation analysis of ctDNA from plasma, including a composite approach of targeted ultra-deep sequencing (n = 25 key HCC genes) incorporating unique molecular barcodes, and Digital Droplet PCR (DDPCR) of the *TERT* Promoter mutation C228 T. Primary endpoint was progression-free survival (PFS) stratified by mutation profiles in ctDNA. Secondary endpoints were overall survival and objective response rate.
Results: We included a total of 121 patients. The most frequent mutations in advanced HCC (n = 85) were TERT promoter (51%), TP53 (32%), CTNNB1 (17%), PTEN (8%), AXIN1, ARID2, KMT2D, and TSC2 (each 6%). TP53 and CTNNB1 mutations were mutually exclusive. Patients with mutations in the PI3 K/MTOR pathway had significantly shorter PFS than those without these mutations after TKI (2.1 versus 3.7 months, p < 0.001, HR for progression or death: 6.7 in multivariate Cox regression, p = 0.01, n = 22), but not after CPI (n = 32). WNT pathway mutations were not associated with PFS, overall survival, or objective response in patients with and without mutations after CPI (n = 32). Serial profiling of ctDNA correlates with treatment response (n = 8).



Conclusion: Mutation calling from ctDNA in advanced HCC detects similar frequencies of mutations compared to those reported in early stages, except lower rates in CTNNB1. Mutations in the PI3 K/MAPK pathway correlate with worse PFS in patients receiving TKIs. We did not find a correlation between WNT/b-catenin pathway mutations and response to CPI, however, our findings need to be further validated in large and prospective investigations.

SAT491

Diagnostic value of brush cytology alone and in combination with tumor marker in malignant biliary stricture

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Background and Aims: Differentiating malignant from benign lesions is an important step in the management of patients with biliary stricture. This makes tissue diagnosis the key step in the evaluation of such patients. Endoscopic retrograde cholangio-pancreaticography (ERCP) based brush cytology sampling is a useful tool in the tissue diagnosis of biliary strictures. The aim of

our study is to determine the yield of brush cytology alone and in combination with tumor maker in patients with suspected malignant stricture.
Method: 68 patients with suspected malignant biliary obstruction based on clinical presentation with altered liver function tests in a cholestatic pattern and evidence of biliary obstruction in the form of stricture or pancreatic/biliary mass on imaging (contrast computerised tomography) underwent ERCP & brush cytology with onsite cytology analysis . The final diagnosis was approved based on the histological examination of the tissue taken surgically or by endoscopic – fine needle aspiration.
Results: A total of 68 cytological specimens were included. The mean age of the patients was (52.03 ± 10.47) years and (51.5%)were males. (52.9%) of the patients had distal CBD stricture. Out of the 52 patients with malignant stricture confirmed with histology , 46 patients had positive brush cytology. The sensitivity and specificity of brush cytology with on site analysis in diagnosing malignant stricture in our study was (80.77%) and 75 % respectively ($p < 0.001$). The sensitivity of brush cytology in diagnosis of malignancy in distal CBD stricture was (92.31%). The sensitivity and specificity of brush cytology in combination with Ca19.9 was (96.2%) and (62.5%) respectively($p < 0.001$).
Conclusion: Brush cytology has high sensitivity and specificity when performed with good technique and with on site analysis of the sample . The accuracy of the test is further enhanced while used in combination with tumor markers. Thus making the notion that brush cytology with on site analysis and in combination with tumor marker is a reliable method of diagnosing malignant biliary strictures

SAT492

miR-486-3p mediates sorafenib resistance through targeting FGFR4 and EGFR in hepatocellular carcinoma

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Background and Aims: HCC is a common malignancy worldwide and surgery or reginal treatments are deemed insufficient for advanced-stage disease. Sorafenib is an inhibitor of many kinases and was shown to benefit advanced HCC patients. However, resistance emerges soon after initial treatment, limiting the clinical benefit of sorafenib and the mechanisms still remain elusive. Thus, this study aims to investigate the mechanisms of sorafenib resistance and to provide possible targets for combination therapies.
Method: Sorafenib resistant cell lines were established by sustained treatment of small dose of sorafenib. qRT-PCR and western blotting were used to measure microRNA and protein levels. Effects of sorafenib was valued by cell viability analysis using Cell Counting Kit-8 assay or real-time cellular analysis. MicroRNA manipulation was performed using RNAi transfection or CRISPR-CAS9 technique. Cell apoptosis analysis was carried out using flowcytometry and TUNEL assay. Cell cycle analysis was conducted using flowcytometry. Binding between microRNA and 3′UTR was verified by Luciferase reporter assay. Over-expressing miR-486-3p in sorafenib resistant animal model was conducted using lentivirus.
Results: Through miRNA sequencing, we found miR-486-3p was downregulated in sorafenib resistant HCC cell lines. The finding was confirmed via qRT-PCR analysis. Cell viability experiments showed increasing miR-486-3p expression could induce cell apoptosis while miR-486-3p knockdown by CRISPR-CAS9 technique could reduce cell apoptosis under sorafenib treatment. Mechanism dissections showed that miR-486-3p mediated sorafenib resistance through targeting FGFR4 and EGFR, which was predicted by online database miRWALK2.0 and verified using luciferase reporter assay. Importantly, FGFR4 or EGFR selective inhibitor could enhance sorafenib efficacy in resistant cells. Clinical data also indicated that miR-486-3p level was downregulated in tumor tissue compared with adjacent normal tissue in HCC patients. Analysis using online database KM-plotter indicated that patients with high expression of miR-486-3p had significantly worse overall survival and disease-free survival. In vivo experiment using sorafenib resistant model demonstrated that miR-486-3p could sensitize tumor to sorafenib treatment.
Conclusion: we found miR-486-3p was an important mediator regulating sorafenib resistance by targeting FGFR4 and EGFR, thus offering a potential target for HCC treatment.

SAT493

Comparative outcomes of laparoscopic and open major liver resection using benchmark article method and propensity score matching method

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Background and aims: To compare the outcomes of major laparoscopic liver resection (LLR) and open liver resection (OLR) for hepatocellular carcinoma (HCC) with two methods.
Method: We retrospectively reviewed a data of 177 patients who underwent major liver resection for HCC (LLR; n = 67 vs. OLR; n = 110). We performed 1:1 propensity score matching (PSM) between two groups and matched 65 patients for both groups. Another comparison was done with already published article as a benchmark after applying similar inclusion and exclusion criteria (LLR; n = 30 vs. OLR; n = 34).
Results: After PSM, there were no significant differences in blood loss (1407.2 ± 2322.7 vs 1071.5 ± 1160.6ml; $P = 0.299$), and transfusion rate (32.2% vs 32.0%; $P = 0.574$) between two groups. The mean operative time was significantly longer in LLR than in the OLR group (418.7 ± 172 vs 335.1 ± 121.6 min; $P = 0.002$). Complication rate (21.5% vs 33.8%; $P = 0.085$) was similar and the mean hospital stay was shorter in the LLR than in the OLR group (11.4 ± 8.5 vs 17.6 ± 21.4 days; $P = 0.009$). After benchmarking method, there were no significant differences in between two groups in terms of blood loss (780 ± 822 vs 947 ± 660.5 ml; $P = 0.382$), transfusion rate (30.0 vs 32.4%; $P = 0.528$), hospital stay (9 ± 3.7 vs 10.4 ± 3.59 days; $P = 0.119$), and complication rate (10.0% vs 20.6%; $P = 0.208$). Operation time (395 ± 166.6 vs 296 ± 68.3 min; $P = 0.002$) was significantly longer in the LLR than in the OLR group. Benchmarking method showed significant loss of number of patients analysed, but results were quite similar to PSM method.
Conclusion: Both methods showed that major LLR was safe compared to major OLR. Benchmarking method can be easily used to compare with data of other published article.

SAT495

Safety and efficacy of lenvatinib in Child-Pugh A and B patients with unresectable hepatocellular carcinoma in clinical practice

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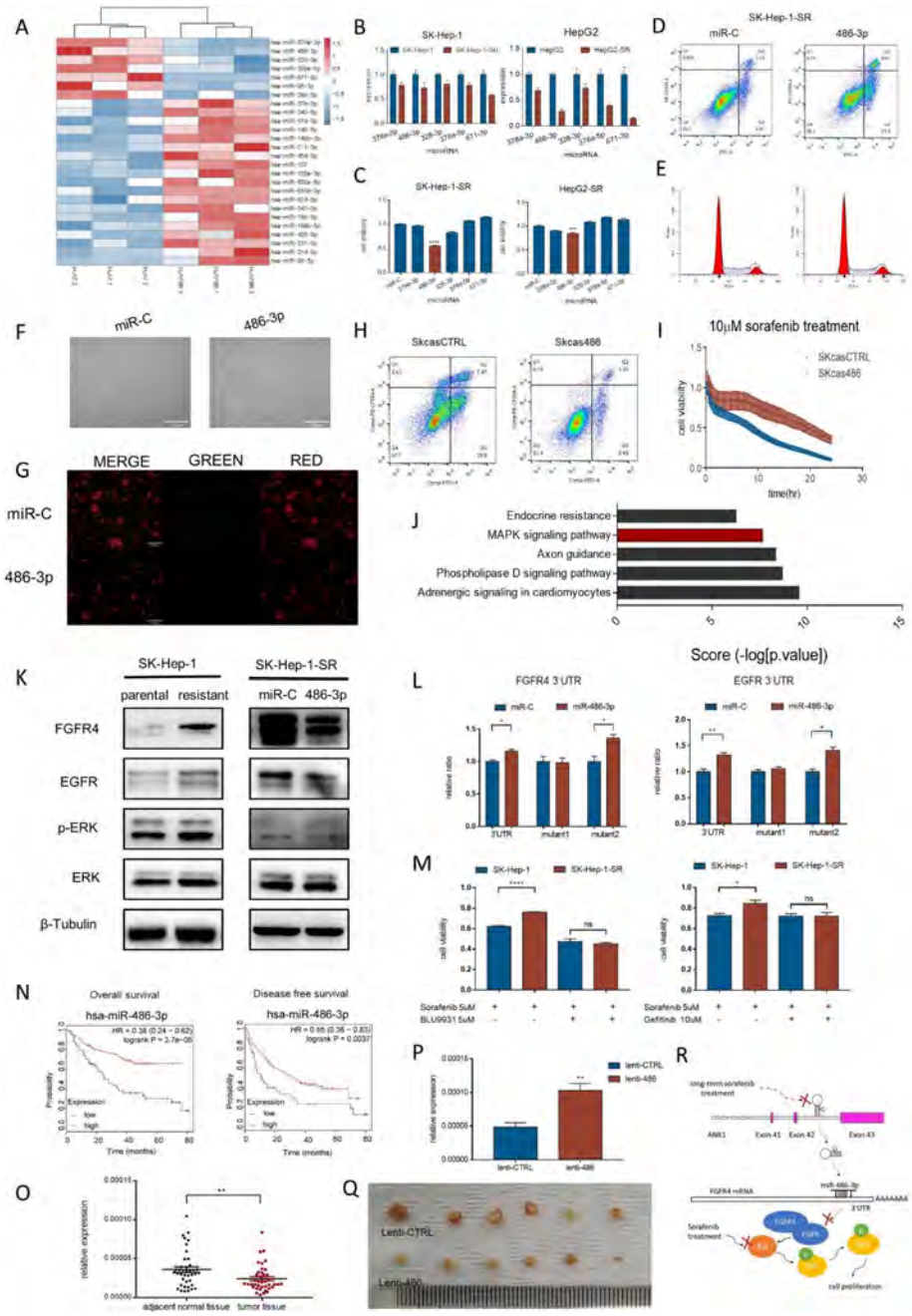

Figure: (abstract: SAT492)

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Background and Aims: Lenvatinib has become available as first-line therapy in patients with unresectable hepatocellular carcinoma (u-HCC). However, factors associated with responses and outcomes to lenvatinib have not been clarified in large scale clinical practice, and the safety and efficacy of lenvatinib in Child-Pugh class B (CPB) patients with u-HCC has not been sufficiently investigated. The aim of this study was to assess the safety, efficacy and prognostic impact of clinical factors in both CPA and CPB patients with u-HCC.
Method: Patients with u-HCC who were treated with lenvatinib at multiple centers in Japan were analyzed retrospectively for treatment outcomes according to their respective CP status. Radiological objective response (OR) was assessed using modified RECIST guidelines.
Results: Baseline demographic parameters were comparable between 127 (70.2%) patients with CPA disease and 54 patients (29.8%) with CPB disease. Eighty-three (45.9%) and 98 (54.1%) cases were noted to have Barcelona clinic liver cancer (BCLC) stage B and C, respectively. Frequency of lenvatinib-related all grade adverse events, including diarrhea (P = 0.037), decreased appetite (P = 0.022), vomiting (P = 0.008) and increased blood bilirubin (P = 0.015) were higher in CPB patients than in CPA patients. Relative dose intensity (RDI) was significantly higher in CPA (0.71) than CPB patients (0.51, P < 0.001). Furthermore, OR rate was markedly higher in CPA (36.2%) than in CPB patients (16.7%, P = 0.0085). In univariate and multivariate analysis, performance status (P = 0.042), CP grade (P = 0.013), des-gamma-

carboxy prothrombin (P = 0.039), RDI (P = 0.0017) and fatigue (P = 0.008) were identified as factors associated with response to lenvatinib treatment. Overall survival (OS) at 12 months was significantly different between CPA (61.4%) and CPB patients (30.5%, P = 0.005). CP grade (P = 0.044), patients with ≥50% liver occupation (P = 0.034), BCLC stage (P = 0.040), α-fetoprotein (P = 0.007), RDI (P = 0.039), hand foot syndrome (P = 0.008) and decreased appetite (P = 0.033) were associated with OS following lenvatinib treatment.
Conclusion: Lenvatinib treatment offers significant benefit in patients with good liver function in real-world practice. The various characteristics identified in this study might be helpful as clinical-predictors of response to lenvatinib and survival in field practice.

SAT496

Analyses of intermediate-stage hepatocellular carcinoma patients receiving transarterial chemoembolization before designing clinical trials comparing transarterial chemoembolization and immune checkpoint inhibitor-based therapies

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Background and Aims: Patients with intermediate-stage hepatocellular carcinoma (HCC) having a high tumor burden exhibit a high frequency of recurrence and progression to advanced stage HCC after transarterial chemoembolization (TACE). Novel promising results from immune checkpoint inhibitors (ICIs) and ICI-based therapies are expected to replace TACE, particularly in patients with HCC having a high tumor burden. This study aimed to evaluate the effectiveness of TACE to design clinical trials and identify limited high-burden populations that could be shifted from TACE to ICI-based therapies.
Method: We retrospectively identified patients with intermediate-stage HCC undergoing TACE from our database. Three subclassification models of intermediate-stage HCC were defined based on the diameter of the maximum tumor and the number of tumors; these models were used to verify clinical outcomes [subclassification model 1, up-to-seven criteria, high burden: largest tumor diameter (cm) + number of tumors >7; subclassification model 2, five-seven criteria, high burden: 4 lesions of size ≥5 cm or >7 lesions; and subclassification model 3, seven lesions criteria, high burden: >7 lesions]. Clinical outcomes were compared between low- and high-burden intermediate-stage HCC and between the different clinical courses reaching a high tumor burden in all subclassification models. We also assessed the ≥6-month durable response rate (DRR) [rate of continuous response (complete or partial objective response) beginning within 12 months of treatment and lasting ≥6 months] according to mRECIST.
Results: Of 1161 newly diagnosed patients with HCC, 316 were diagnosed with intermediate-stage HCC and underwent TACE. The median overall survival of the high tumor burden intermediate-stage patients was not significantly different according to the clinical course reaching a high tumor burden in all subclassification models. The prognosis of high-burden patients after initial TACE was poor compared with that of low-burden patients for two models (except for model 1). In all models, high-tumor burden patients showed a poor DRR of ≥ 6 months and a poor prognosis after TACE. Moreover, patients with confirmed durable response of ≥ 6 months showed better survival outcomes for high-tumor burden intermediate-stage HCC.
Conclusion: Our results demonstrate the basis for selecting a population that would not benefit from TACE and setting a DRR of ≥6 months as an alternative endpoint when designing clinical trials comparing TACE and ICI-based therapies.

SAT497

High rate of hepatitis B virus S-integrated human extra spindle pole bodies like 1 fusion gene is detected in hepatitis B virus-related liver cancer patients: a Chinese case-control study

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Background and Aims: It has been shown that the integration of hepatitis B virus (HBV) gene into the host genome is a high-risk factor for hepatocellular carcinoma (HCC) development. However, the relationship between HBV S-integrated human Extra Spindle Pole Bodies Like 1 (ESPL1) gene and HCC is unknown. This study was designed to detect HBV S-integrated human ESPL1 fusion gene in HCC patients for potentially developing this fusion gene as a biomarker for HCC diagnosis.
Method: Nineteen and 70 chronic hepatitis B (CHB) patients were recruited to the experimental and control groups, respectively, and both groups underwent an effective nucleoside/nucleotide analogs (NUCs) therapy and follow-up for HCC occurrence for up to 11 years. HCC tissues were obtained by surgical resection from the experimental group, while liver tissues were collected by liver biopsy in the control group prior to NUCs treatment. Alu polymerase chain reaction (PCR) was used to assess HBV S gene integration in the liver tissues from both groups. HBV S-integrated human ESPL1 fusion gene was then detected in the patients with HBV S gene integration by using the gene database.
Results: We observed that all CHB patients in the experimental group developed HCC, whereas no HCC was diagnosed in the control group. HBV S gene integration was identified in 12 out of 19 HCC tissues in the experimental group with a detectable rate of 63.2% (12/19), which was significantly greater than that of 15.7% (11/70) in the control group (P = 0.000). We further showed that HBV S-integrated human ESPL1 fusion gene was detected in 8 patients with a rate of 66.7% (8/12) among the 12 HCC patients with HBV S gene integration in the experimental group, whereas the fusion gene was not detectable in any one among the CHB patients in the control group (P = 0.001) (Fig 1).

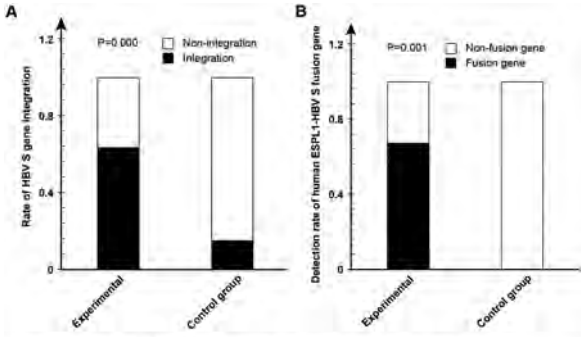

Figure 1. Detection rate of HBV S gene integration and human ESPL1-HBV fusion gene in the experimental and control groups. (A) The comparison of HBV S gene integration in both the experimental and control groups by chi-square test of four-fold table. Our data indicate that HBV S gene integration rate is significantly higher in the experimental group than that in the control group (P=0.000). (B) The comparison of the detection rate of the human ESPL1-HBV S fusion gene between the experimental and control groups by Fisher's exact probability. The data show that the detection rate of human ESPL1-HBV S fusion gene is 66.7% in the experimental group as compared with 0% in the control group (P=0.001).

Conclusion: This research demonstrates a high detectable rate of HBV S-integrated human ESPL1 fusion gene in HBV-related HCC patients and shows that this fusion gene is associated with HCC development in CHB patients. These findings suggest that HBV S-integrated human ESPL1 fusion gene may potentially serve as a biomarker for early detection of HCC in the HBV-infected populations.

SAT498

Treatment decision for hepatocellular carcinoma ?5cm: surgical resection or microwave ablation

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Background and Aims: Thermal ablation challenges the status of surgical resection on small hepatocellular carcinoma (HCC) treatment, while its therapeutic outcomes for larger lesions are still in debate. This study aims to compare long-term outcomes of surgical resection (SR) and microwave ablation (MWA) and give clues to treatment decision for HCC ≤5 cm.
Method: This retrospective study evaluated 639 patients with primary HCC (1 nodule <5 cm or 3 nodule <3 cm) who underwent curative SR or MWA from January 2008 to December 2015. Overall survival (OS), free intrahepatic recurrence (FIR) and disease-free survival (DFS) were compared using propensity score matching to control for potential confounders. Co-variables associated with OS and DFS were identified. The risk of death and tumor progression in HCC patients received SR versus MWA was compared.
Results: 256 Patients were well matched according to baseline characteristics. The OS rate of 1-, 3-, 5-year were estimated to be 94.9%, 81.6%, 70.6% in MWA group and 98.4%, 89.1%, 77.8% in SR group (P = 0.00). No significant differences were found in terms of DFS and FIR rate. In subgroup analysis, the OS rate of 1-, 3-, 5-year was similar in two groups for tumors smaller than 3 cm (P = 0.24), while the OS rate was higher in SR group than in MWA group for tumors between 3 cm to 5 cm(P = 0.01). Similar results were found in further subgroup analysis of MWA, anatomic and non-anatomic SR group, and anatomic SR group showed longest OS rate. Major complication rate was similar while post-treatment stay was significantly longer in SR group.
Conclusion: MWA provided non-inferior survival outcomes to SR in HCC≤3 cm. For larger tumors ≤5 cm, more techniques such as 3D visualization platform are needed to enhance the therapeutic outcomes.

SAT499

Chlorogenic acid decreases malignant characteristics of hepatocellular carcinoma cells by inhibiting DNMT1 expression

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Background and Aims: Hepatocellular carcinoma (HCC) is the most common malignant tumor of the adult liver, exhibiting rapid progression and poor prognosis. DNA methylation is an essential epigenetic event in gene-expression regulation processes; it may lead to cancer. Chlorogenic acid (CGA), a polyphenol, has several biological activities, including the suppression of liver cancer cell invasion and metastasis. However, the mechanisms underlying the CGA-mediated regulation of DNA methylation are still unclear.
Method: The human HCC HepG2 cells were treated with a positive control drug 5-azacytidine (5 -AZA) or varying doses of CGA. DNA methyltransferase 1 (DNMT1) protein levels and other relevant proteins were evaluated using western blotting and immunocytochemistry. Cell-cycle analysis was performed by flow cytometry-based PI staining, and cell viability was assessed using 3-(4,5 -dimethylthiazol- 2 -yl)- 2,5 -diphenyltetrazolium bromide assay. The transwell invasion and wound healing assays were used to

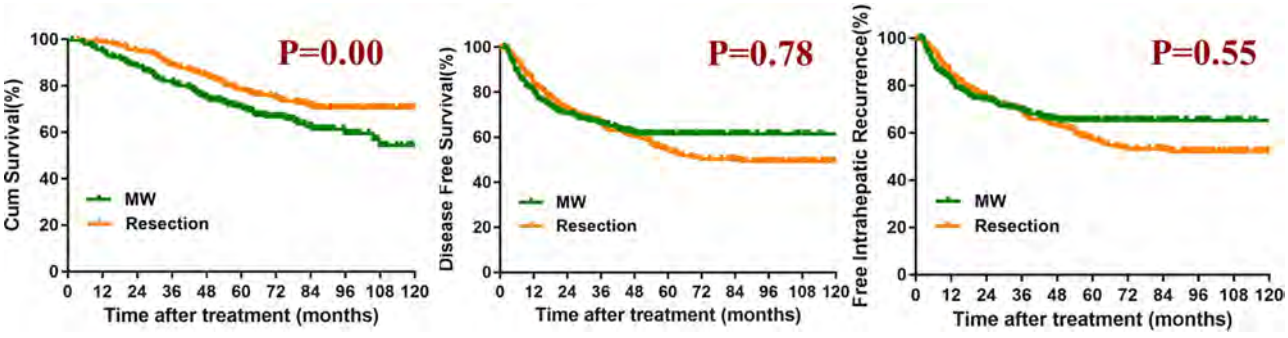

Figure 1: (abstract: SAT498): Comparison of OS(a), DFS(b) and FIR(c) between MWA group (N = 256) and surgery group (N = 256).

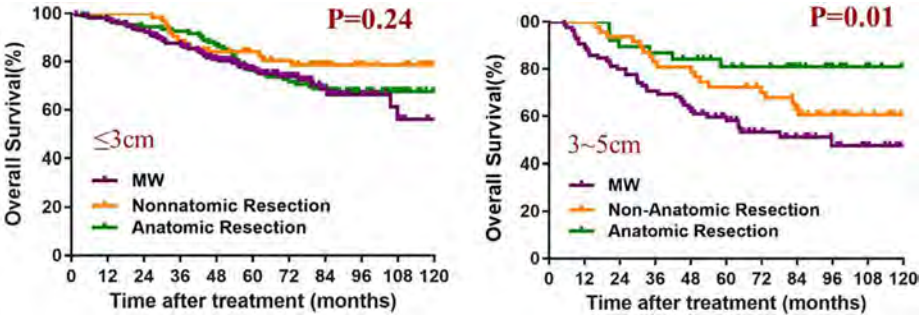

Figure 2: (abstract: SAT498): Comparison of OS(a), DFS(b) and FIR(c) in subgroup analysis.

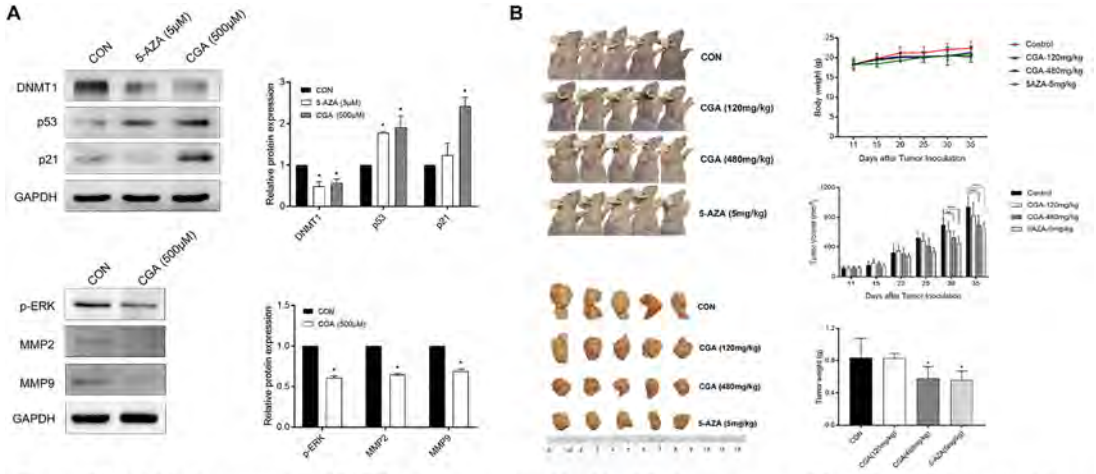

Figure. CGA inhibits the expression of DNMT1 and up-regulate p53, p21waf/Cip1, to suppress HCC cell proliferation and inhibits the expression of ERK1/2 and MMP2/9 to suppress HCC growth (A), CGA reduces HepG2 tumor xenograft's weight and volume (B). *p < 0.05, **p < 0.01, ***p < 0.001.

Figure: (abstract: SAT499)

evaluate cell migration and invasion. The in vivo anticancer effect of CGA was evaluated in immunodeficient HepG2 xenograft nude mouse models.

Results: Our results showed that CGA inhibited the proliferation, colony formation, invasion, and metastasis of HepG2 cells by down-regulating the DNMT1 protein expression, which enhanced p53 and p21 activity, resulting in significantly reduced cell proliferation and metastasis. Moreover, CGA inactivated extracellular signal-regulated kinases 1/2 and reduced matrix metalloproteinase- 2 and- 9 expression in HepG2 cells. And in vivo, CGA treatment inhibited growth of HepG2 xenograft tumors, at both 120 and 480 mg/kg of CGA causing reduction in tumor weight and tumor volume.

Conclusion: CGA can suppress liver cancer cell proliferation, invasion, and metastasis through several pathways in vivo and in vitro. CGA could serve as a candidate chemopreventive agent for HCC.

SAT500

Protective role of aspirin chronic assumption in patients treated with sorafenib for hepatocellular carcinoma

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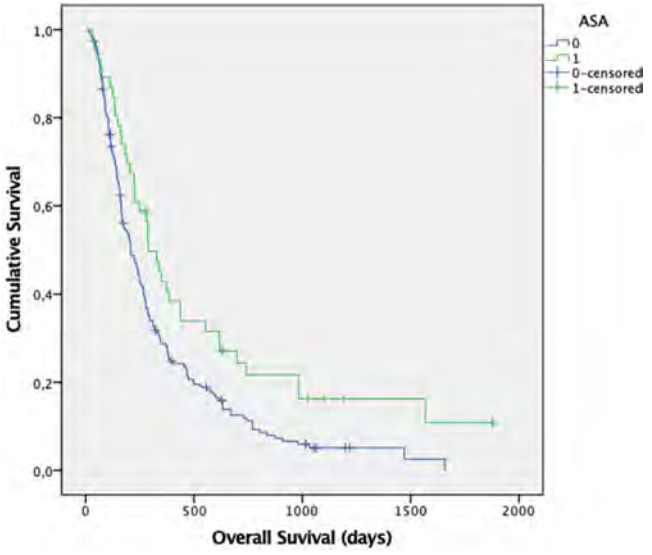
Background and Aims: Hepatocellular carcinoma (HCC) is the most common primary liver cancer that usually develops in a microenvironment characterized by chronic liver inflammation. Several in vitro and mouse-model studies have shown the pivotal role of platelets in cancerogenesis, tumor cell migration and invasion. Platelets have also been reported to antagonize the effect of tyrosine kinase inhibitors such as sorafenib and regorafenib. The protective role of anti-platelet agents has largely been studied in different cancer types, including HCC. In particular, in vitro studies have shown the effect of aspirin in decreasing tumor cell proliferation, increasing sensitivity to chemotherapeutics and inducing apoptosis. All these findings suggest a possible synergy between the chronic inhibition of platelets activity by aspirin and sorafenib in patients with advanced HCC.

Method: We retrospectively analyzed baseline and follow-up clinical data of 232 patients who consecutively received sorafenib treatment from January 2008 and December 2017. Patients were divided in two groups according to the daily assumption of aspirin or not (46 and 186 patients, respectively). In order to evaluate the synergic activity of aspirin and sorafenib, in the OS analysis, patients who received a second-line treatment were censored when starting the new therapy.



Results: Baseline characteristics, adverse events and radiological response were consistent across groups. The OS survival of patients treated with aspirin was significantly higher (10.3 vs 7.4 months, p = 0.008). Multivariate time-dependent Cox regression analysis confirmed aspirin treatment as an independent protective factor (HR 0.658; 95%CI 0.460–0.941) when compared to other already established predictors of survival such as AFP >400 ng/ml (HR 1.341; 95%CI 0.977–1.841; p = 0.070), Performance Status 1 (HR 1.320; 95%CI 0.951–1.830; p = 0.097), neoplastic thrombosis (HR 1.422; 95%CI 1.065–1.898; p = 0.017), extrahepatic spread (HR 1.227; 95%CI 0.915–1.646; p = 0.172) and dermatological adverse events (HR 0.579; 95%CI 0.437–0.767; p < 0.001).

Conclusion: Accordingly with data from pre-clinical studies, chronic assumption of aspirin seems to have a protective role also in patients with advanced HCC. A proven synergic effect between aspirin and sorafenib needs to be confirmed with further studies.

SAT501

A lncRNA-associated ceRNA regulatory network in MVI positive hepatocellular carcinoma influences their sensitivity to sorafenib

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Background and Aims: Microvascular invasion (MVI) is a histological feature of hepatocellular carcinoma (HCC) related to aggressiveness. But different sensitivity to first line targeted drug, sorafenib, in MVI$^+$ HCC has been observed. Long noncoding RNAs (lncRNAs) can act as microRNA (miRNA) sponges to regulate protein-coding gene expression; so lncRNAs are considered as a major part of competitive endogenous RNA (ceRNA) network and have attracted growing attention. We explored the regulatory mechanisms and functional roles of lncRNAs as ceRNAs in MVI$^+$ HCC, and ceRNA network's potential impact on prognosis and sensitivity to sorafenib in MVI$^+$ HCC patient.

Method: We studied the expression profiles, prognostic value of lncRNA, miRNA, and mRNA from MVI$^+$ HCC patients, established a prognosis-related network of dysregulated ceRNAs and analyzed its role in sensitivity to sorafenib and radiomics features by bioinformatics methods.

Results: A ceRNA network including 13 lncRNAs, 3 miRNAs, and 2 mRNAs specific to MVI+ HCC was established. 6 lncRNAs (ARHGEF7-AS1, ATP2B2-IT1, LINC00330, MUC2, TLR8-AS1 and ZNF385D-AS1), 2 miRNAs (has-mir-206 and has-mir-373) and two mRNAs (PAX3, SIK1) were prognostic biomarkers for MVI$^+$ HCC. PAX3 was an unfavorable prognostic gene (HR = 1.9, 95%CI 1.01 ~ 3.60), while SIK1 favored the prognosis (HR = 0.4, 95%CI 0.19 ~ 0.85). PAX3 as a stratification in recurrence predicting model was used to identify MVI$^+$ HCC with high or low recurrence risk. Datamining into the dataset of phase 3 STORM trial showed no difference in the influence of PAX3 level on the outcome between sorafenib HCC group and placebo HCC group. However, deep datamining into GDSC dataset revealed our high PAX3 group in MVI$^+$ HCC related to resistance to sorafenib (P = 0.0039). Radiomics features were extracted from CT of MVI$^+$ HCC, and texture analysis in MVI$^+$ HCCs is ongoing.

Conclusion: The proposed ceRNA network may help elucidate the regulatory mechanism by which lncRNAs function as ceRNAs and contribute to the pathogenesis of MVI in HCC. Importantly, the candidate lncRNAs, miRNAs, and mRNAs involved in the ceRNA network have shown to be potential therapeutic targets and prognostic biomarkers for MVI$^+$ HCC. PAX3 might play a vital role in the mechanism of sorafenib resistance in MVI$^+$ HCC, exclusively, this aggressive HCC subtype. The ongoing experiments on radiomics might add potent supports to identify sorafenib sensitive MVI$^+$ HCC.

SAT502

In vivo performance of PEG-coated gold nanoparticles mediated ultrasound guided radiofrequency ablation: a pilot study in swine

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Background and Aims: Radiofrequency ablation (RFA) is the first line treatment option for patients with small hepatocellular carcinoma and a recommended treatment modality for patients with hepatic metastases judged to be unfit for surgical intervention. However, RFA is still used mainly for lesions <3 cm, and despite all great advancements the ablation zone remains limited in volume. Gold nanoparticles offer the potential to heat tumour tissue selectively at the cellular level by non-invasive interaction with radiofrequency energy delivered externally. The objective of this study was to investigate the effects of polyethylene glycocol (PEG) coated gold nanoparticles intratumoral delivery on ablation zone volumes during in vivo RFA of porcine liver.

Method: This prospective study was performed following institutional animal care and use committee approval. RFA was performed in liver in ten Sus scrofa domesticus swine. PEG coated gold

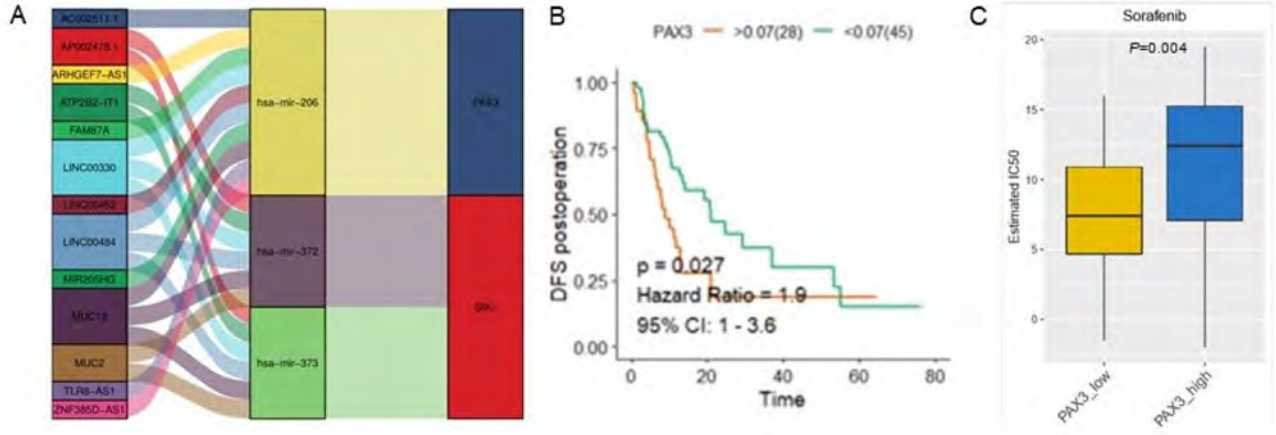

Figure: (abstract: SAT501)

nanoparticles (10 millilitres of solution for each ablation with a concentrations of 1×10^{11} and 1×10^{7} nanoparticles/ml) were injected through the radiofrequency antennae during ablation. Physiological saline (10 millilitres for each ablation) was used as control. Ten minutes after ablation contrast enhanced ultrasound (CEUS) was performed to evaluate the necrosis volume. Animals were kept under close medical observations for 5 days. On day 5 another CEUS examination was performed and animals were using a sodium pentobarbital solution. Treated tissues were explanted and the necrosis volume was measured using callipers. Haematoxylin and eosin (H&E) staining was also performed for histological analysis.

Results: A total of 30 ablations were performed in the liver. The use of PEG coated gold nanoparticles significantly increased ablation zone volumes (13.61 cm^3 versus 5.26 cm^3, $p < 0.001$). The increase of ablation zone volumes was not dose dependently (13.61 cm^3 versus 11.84 cm^3, $p = 0.17$). There was no difference between ablation zone volumes assessed by CEUS immediately after ablation compared to CEUS performed 5 days after ablation ($p = 0.34$). H&E staining showed no differences in the transition zone (the zone between coagulative necrosis and normal parenchyma) between physiological saline or nanoparticles enhanced RFA.

Conclusion: The use of PEG coated gold nanoparticles significantly increased mean ablation zone volumes following direct intratumoral RFA in a porcine model. To our knowledge this is the first study dealing with direct heating of PEG-coated nanoparticles by RF energy. However, the positive finding from our study warrants further investigations.

SAT503

The "six-and-twelve" score in a prospective cohort of patients with hepatocellular carcinoma treated with trans-arterial chemoembolization following a fixed schedule

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Background and Aims: Trans-arterial chemoembolization (TACE) is the standard of care treatment for patients with hepatocellular carcinoma (HCC) at BCLC-B stage or BCLC-0/A without other options while some BCLC-B patients receive systemic therapy as first-line treatment according to the stage migration concept. Several tools to better define the prognosis of TACE candidates have been proposed. The "Six-and-twelve" score stratifies TACE candidates into 3 strata (G1≤6; G2 >6 y≤12; G3>12) according to the sum of the biggest target lesion size and the number of lesions. It stratifies overall survival (OS) with a reported C-index of 0.67 in Asian patients (ES ASI).

To assess the performance of the "Six-and-twelve" score to predict the OS in a prospective Western cohort of patients treated with fixed-schedule TACE at 0,2 and 6 months and thereafter every 6 months until untreatable progression.

Method: All TACE candidates at Hospital Clinic of Barcelona between 01/2014 and 03/2017 were prospectively included and the OS was analyzed according to the "Six-and-twelve" score in the whole cohort and in each BCLC stage.

Results: of the 105 included patients (HCV 51.89%, Child-Pugh-A 92.45% and BCLC-A/B 46/59), 90 received at least one treatment session. The median follow-up of the whole cohort was 24.4 months and the median OS (mOS) was 35.5 moths (IC95% 28.7– 42.6).

The "Six-and-twelve" score was G1 in 60 patients and G2 in 30 but no patient had G3. The mOS of G1 patients was 42.6 months (IC95% 29.8–49.0) and of G2 de 29.0 (IC95% 21.1–36.2) with a *p*-value = 0,037 and a *C-index* of 0.54 (IC95% 0.46–0.62). Thirty-eight G1 patients were BCLC-A and 32 BCLC-B, while only 5 of the 46 BCLC-A patients were G2. When the "Six-and-twelve" score was applied in each BCLC stage, the mOS was not different [(BCLC-A ($p = 0.39$), HR = 2.07 (IC95% 0.66–6.44); BCLC-B patients ($p = 0.82$), HR = 0.85 (IC95% 0.42–1.7)]. Specifically, the mOS of G1 and G2 were 44.0 months (IC 95% 36.3 - NE) and 36.2 (17.8 - NE) in BCLC-A patients and 27.6 (IC 95% 22.3–49.0) and 28.7 (IC 95% 18.4–35.5) in BCLC-B, respectively.

Conclusion: This study confirms the ability of the score to predict OS according but with a very low performance (*C-index* = 0.54). The score is not able to stratify TACE candidates in each BCLC stage. Thus, its clinical-practice usefulness remains limited although it could be considered as a potential tool to stratify TACE candidate in clinical trials.

SAT504

Hepatic arterial infusion chemotherapy combined with sorafenib versus sorafenib monotherapy in advanced hepatocellular carcinoma: a systemic review and meta-analysis

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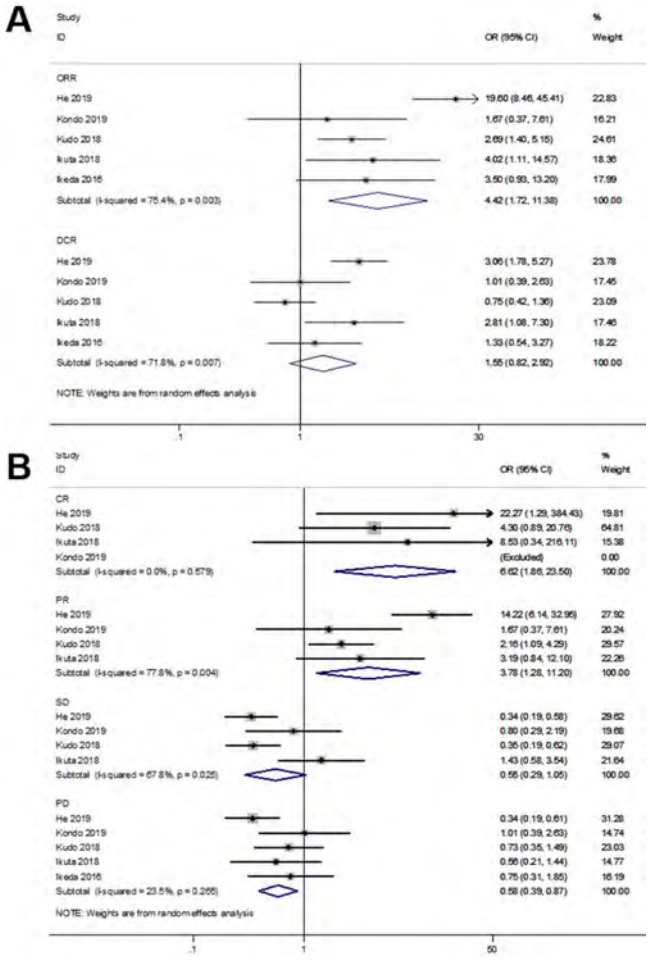
Background and Aims: Recent studies demonstrated that as an alternative therapy to sorafenib, hepatic arterial infusion chemotherapy (HAIC) has promising outcomes in treatment for advanced hepatocellular carcinoma (HCC). However, it remains controversial whether the combination of HAIC and sorafenib is superior to sorafenib monotherapy. This study aimed to compare the efficacy and safety of HAIC+sorafenib versus sorafenib alone.

Method: A comprehensive search of online databases was performed from January 2009 to November 2019. All outcomes of treatment efficacy and safety were extracted and synthesized. A meta-analysis and relative subgroup analysis were conducted.

Results: A total of 724 patients (HAIC+sorafenib 353 vs sorafenib 371) from 5 studies, including 4 randomized controlled trials and 1 cohort study, were included in this meta-analysis. Compared to sorafenib monotherapy, HAIC + sorafenib has a higher objective response rate (OR:4.42, 95% CI: 1.72~11.38, P = 0.002). Similar results in higher complete response (OR: 6.62, 95%CI: 1.86~23.50, P = 0.003), partial response (OR: 3.78, 95%CI: 1.28~11.20, P = 0.016), and less progressive disease (OR: 0.58, 95%CI: 0.39~0.87, P = 0.009) were observed. However, there is no significant difference on overall survival (OS) (HR: 0.67, 95%CI 0.41~1.07, P = 0.094), except for patients with lower AFP level (HR: 0.72, 95%CI 0.52~0.99, P = 0.042). Meanwhile, HAIC +sorafenib leads to an increased tendency on adverse events including anemia, neutropenia, anorexia and nausea.



Conclusion: This meta-analysis revealed that the combination therapy of HAIC and sorafenib is superior in short-term benefits or objective response rate. However, it fails to prolong overall survival and even increased the risk of adverse events. High-quality studies should be conducted in the future to further illustrate this issue.

SAT505

Dexamethasone prophylaxis of postembolization syndrome after transcatheter arterial chemoembolization: a randomized, double-blind, placebo-controlled study

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Background and Aims: Postembolization syndrome is the most frequent adverse event of transcatheter arterial chemoembolization (TACE) in patients with hepatocellular carcinoma. We evaluated single dose of dexamethasone efficacy at preventing postembolization syndrome.

Method: This study include patients with HCC without macrovascular invasion who had a Child–Pugh score of A or B and no distant metastasis. Patients were randomly assigned to either a dexamethasone 8 mg intravenous single dose one hour prior to TACE or a placebo (saline). The primary outcome was a negative result of post-embolization syndrome (PES), which was defined as score <2 of Southwest oncology group toxicity coding(SWOG) using fever, nausea, vomiting and pain to calculated. And the secondary end point was duration of admission between two groups.

Results: From September 2017 to October 2019, 100 patients were randomly assigned 1:1. Under intention-to-treat analysis, 49 patients were randomly assigned to the dexamethasone group and 51 to the placebo. Both groups were comparable for baseline characteristics. The negative PES rate was greater with the dexamethasone group than with the placebo regimen (65.3% vs. 37.3%; P = 0.005) (Figure 1). Mean SWOG PES was 2.14 (95% CI 1.41-2.8) versus 3.71 (95% CI 2.97–4.45) between dexamethasone group and placebo group respectively. More than grade 2 fever was higher in placebo group (49.1% vs 18.4%; P < 0.001). The patients with ≥1 grade Common Terminology Criteria for Adverse Events (version 4.0) incidence of pain, nausea and vomiting were 56%, 51%, and 19% in the placebo group and 36%, 30%, and 14% in the dexamethasone regimen, respectively.The median duration of admission were 4 days (IQR 3–7 days) in patients receiving the placebo same as those receiving the dexamethasone group (IQR 3-5 days; P = 0.245). The dexamethasone regimen was generally well tolerated by HCC patients including those with well-controlled diabetes mellitus and those with hepatitis B virus infection.

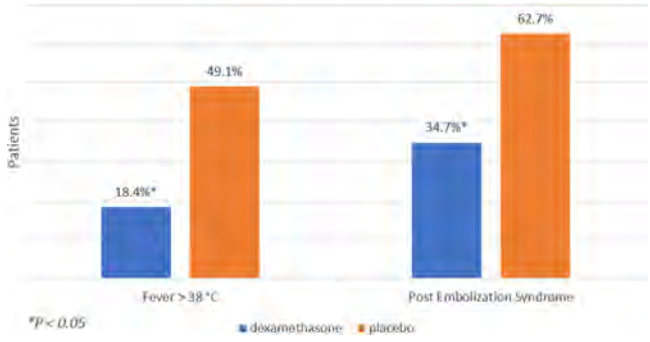

Figure: The incidences of fever and post-embolization syndrome (PES)

Conclusion: Single dose dexamethasone was more effective than the placebo at preventing post-embolization syndrome (PES) in patients with HCC and was generally well tolerated.

SAT507

Association between curative treatment after transarterial radioembolization and better survival outcomes in patients with hepatocellular carcinoma

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Background and Aims: Transarterial radioembolization (TARE) is one of the therapeutic options for hepatocellular carcinoma (HCC). This study aimed to investigate the predictors and prognostic values of achieving curative treatments after TARE.

Method: Overall, 143 patients with intrahepatic HCC treated with TARE between 2011 and 2017 were recruited from two Korean tertiary institutes. Subsequent curative treatment was decided by the physician.

Results: The median age of the study population was 65.0 years. Twenty-seven (18.9%) patients received curative treatments (resection in 16, transplantation in 9, and ablation in 2) after TARE, who were likely to be younger (median 58.5 vs. 69.2 years) and less likely to have hypertension (40.7% vs. 62.9%) than those without curative treatments (all p < 0.05). In multivariate analysis, younger age (<65 years) (hazard ratio [HR] = 9.295, p < 0.001) and alpha-fetoprotein (AFP) of ≤200 ng/mL (HR = 4.246, p = 0.017) independently predicted the increased probability of achieving curative treatment after TARE. Curative treatment after TARE (HR = 0.089, p = 0.023), tumor burden

of >50% (HR = 5.690, p = 0.003), portal vein thrombosis (HR = 5.635, p = 0.002), and progressive disease based on the modified response evaluation criteria in solid tumors (mRECIST) criteria at 3 months after TARE (HR = 9.875, p < 0.001) independently predicted the risk of mortality. The cumulative survival rate of patients with curative treatment was significantly higher than that of patients without (p < 0.001 by log-rank test).

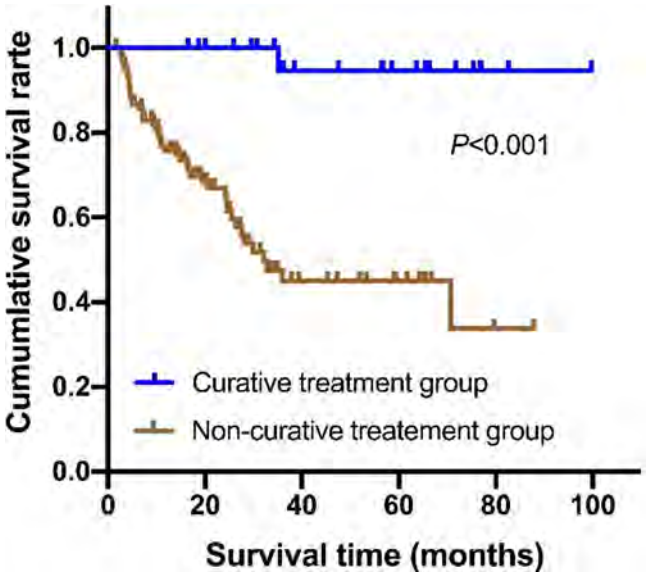

Figure: Kaplan-Meier analysis for overall survival.

Conclusion: Younger age than 65 years and AFP of ≤200 ng/mL independently predicted the increased probability of achieving curative treatment after TARE, and the curative treatment after TARE provided a survival benefit in patients with intrahepatic HCC.

SAT509

The real-world systemic sequential therapy of sorafenib and regorafenib for advanced hepatocellular carcinoma: a multicenter retrospective study in Korea

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Background and Aims: Regorafenib has been proved as 2nd line systemic therapy for hepatocellular carcinoma (HCC) patients through phase III trial. We analyzed the real-world data to assess clinical efficacy and safety.
Method: This study was a multicenter, non-comparative, retrospective cohort study. Between July 2017 and May 2019, 133 patients with HCC who received regorafenib after sorafenib therapy were eligible for inclusion in this study. Tumor response was assessed according to modified RECIST criteria. We evaluated time to progression (TTP), progression-free survival (PFS) and overall survival (OS) of regorafenib therapy including prediction factors for prognosis.
Results: Their median age was 60 years, and most patients (82%) were male. Hepatitis B virus infection (68.4%) was the most common etiology of HCC. Most of patients (98.5%) were classified as Child-Pugh A except 2. Eighty-four percent of patients had extrahepatic metastasis and Vascular invasion was presented in 45.1%. Three patients (2.7%) achieved complete response and 11 (9.8%) patients had a partial response resulting in objective response rate 12.5% in 112 available patients for response assessment. The disease control rate (DCR) was 34.8%. Median treatment duration of regorafenib was 2.6 months (1.5–4.7 months). During follow up, 38 patients died. On regorafenib, the median OS was 10.0 months (95% CI, 8.4–11.6), the median PFS survival was 2.7 months (95% CI, 2.5–2.9 months), and the median TTP was 2.6 months (95% CI, 2.4–2.8). The OS rate from the start of regorafenib at 6 months and 1 year were 71.2%, and 38.7%. In multivariate analysis, Child-Pugh score >5 (HR 3.037 95% CI 1.46–6.314; p = 0.003), AFP >400 ng/ml (HR 5.9; 95% CI 2.608–13.349; p < 0.001), and TTP on sorafenib ≥ median (HR 0.441; 95% CI 0.310–0.629; p < 0.001) were independently associated with OS. In exploratory analysis from the time of sorafenib administration, the median OS from sorafenib administration was 25.8 (95% CI 8.7–42.9 months). The 1 year and 2years survival rate were 79.5% and 53.1%.
Conclusion: Regorafenib was effective in patients with advanced HCC who failed first-line sorafenib in real-life setting, consistent with previous clinical trial. Regorafenib may improve the prognosis of patients who had longer TTP on previous sorafenib therapy.

SAT510

Multicenter, real-world experience with lenvatinib for patients with advanced hepatocellular carcinoma in Japan

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Background and Aims: Lenvatinib has been recently approved as a first-line systematic therapy for patients with advanced hepatocellular carcinoma (HCC) based on the results of the phase 3 clinical trial REFLECT. However, this trial did not enroll patients with a history of systemic chemotherapy including sorafenib and regorafenib, bile duct invasion, and main portal vein invasion (Vp4). This real world multicenter study aimed to investigate the efficacy and safety of lenvatinib for these patients.
Method: Patients who were administered lenvatinib for advanced HCC between April 2018 and July 2019 were enrolled. In principle, the treatment response and safety were evaluated via dynamic CT or MRI every 2 months until radiological disease progression. We evaluated treatment response in accordance with mRECIST. Further analysis by stratifying patients according to compliance and non-compliance with the REFLECT inclusion criteria was conducted.
Results: A total of 105 patients were included. More than 60% (64/105) did not meet the REFLECT inclusion criteria. In total, 11 (10.5%), 42 (40.0%), 38 (36.2%), and 8 (7.6%) showed complete response, partial response, stable disease, and progressive disease, respectively. The overall objective response rate was 50.5%. The objective response rate (p = 0.1853) was similar between patients who did and did not meet the REFLECT inclusion criteria. Moreover, the progression free survival was 10.3 months and 9.8 months, respectively (Hazard Ratio:1.087, 95% CI:0.593–1.686, p = 0.7831). The safety profile was also similar between the patients.
Conclusion: Lenvatinib showed high response rate and tolerability for patients with advanced HCC. Favorable outcomes were similarly observed even in patients who did not meet the REFLECT inclusion criteria.

SAT511

Prognostic value of alpha-fetoprotein in patients achieving complete response to transarterial chemoembolisation for hepatocellular carcinoma

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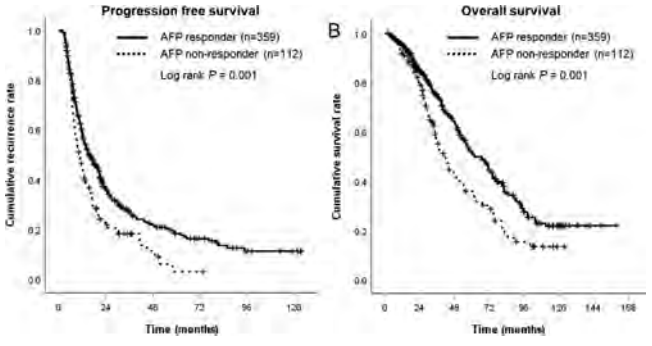
Background and Aims: Alpha-fetoprotein has been used as a diagnostic and prognostic marker in patients with hepatocellular carcinoma (HCC). We investigated the prognostic value of AFP in patients with HCC who achieved complete response (CR) after transarterial chemoembolisation (TACE).

Method: Between 2005 and 2018, 890 patients with HCC who achieved CR according to the mRECIST criteria after TACE as the first-line anticancer treatment were recruited from eight Korean tertiary, academic institutes for this retrospective, multicentre, cohort study. An AFP responder was defined as a patient with an elevated AFP level showing >50% reduction in AFP level after TACE (>10 ng/mL).



Results: During follow-up after CR, 473 (53.1%) patients showed HCC recurrence and 417 (46.9%) died. Before TACE, 305 (34.3%) patients had multiple tumours, 219 (24.6%) patients had a maximal tumour size >3 cm and 22 (2.5%) patients had portal vein tumour thrombosis. On achievement of CR after TACE, the median AFP level was 6.36 ng/mL. The median progression-free survival (PFS) and overall survival (OS) were 16.3 (interquartile range [IQR] 7.9–41.6) and 62.8 (IQR 34.9–103.6) months, respectively. In multivariate analysis, AFP at CR >20 ng/mL was associated with a shorter PFS (hazard ratio [HR] = 1.403, 95% confidence interval [CI] 1.167–1.686) and OS (HR = 1.310, 95% CI 1.050–1.636), together with multiple tumours (HR = 1.518 [95% CI 1.262–1.827] and 1.614 [95% CI 1.307–1.993], respectively). Of 471 patients with AFP >10 ng/mL before TACE, 359 (76.2%) were AFP responders, showing higher median PFS (15.5 [IQR 12.2–18.8] vs. 10.5 [IQR 8.1–12.9] months, respectively) and OS (61.8 [IQR 52.3–71.3] vs. 41.4 [IQR 33.6–49.2] months, respectively) compared to non-responders (both p = 0.001, log rank test). In multivariate analysis, AFP non-response was independently associated with shorter PFS (HR = 1.375, 95% CI 1.077–1.756), together with Barcelona-Clinic-Liver-Cancer Stage B and C (vs. A) (HR 1.377, 95% CI 1.027–1.847) and multiple tumours (HR 1.317, 95% CI 1.022–1.697), and also with shorter OS (HR = 1.406, 95% CI 1.056–1.872), together with a higher bilirubin level at CR (HR 1.439, 95% CI 1.263–1.640).

Conclusion: Low AFP and AFP response were still good predictors of recurrence and OS after achievement of CR by TACE. Therefore, AFP and its response should be used for more detailed risk stratification even after achieving CR following TACE.

SAT513

Updated data from an ongoing study with ADP-A2AFP spear T-cells

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Background and Aims: Genetically engineered affinity-enhanced autologous SPEAR T-cells (AFPc332T-cells) directed towards the HLA-A*02 are being tested in an ongoing Phase 1 trial to evaluate safety and antitumor activity in patients with hepatocellular carcinoma (HCC; NCT03132792).

Method: In this first-in-human study in HCC, patients must be HLA-A*02:01$^+$ or 02:642$^+$ and have AFP expression by immunohistochemistry (IHC) at ≥1+ in ≥20% HCC cells or serum AFP ≥400 ng/ml, and ≤5% IHC AFP in non-cancerous liver tissue. Up to 24 patients will be enrolled using a modified 3+3 design. In Cohorts 1 and 2, lymphodepletion consists of fludarabine (FLU) 20 mg/m^2 and cyclophosphamide (CY) 500 mg/m^2 QD for 3 days. For Cohort 3, lymphodepletion consists of FLU 30 mg/m^2 per day for 4 days and CY 600 mg/m^2 QD for 3 days. Following lymphodepletion with FLU and CY, the target transduced cell doses for Cohorts 1–3 are 0.1×10^9, 1×10^9, and 5×10^9 cells, respectively. Cohort expansion will occur at maximum tolerated dose and may allow doses up to 10×10^9 transduced cells.

Results: As of 14 October 2019, 2 patients were treated in Cohort 1 (previously reported), and 3 in Cohort 2. Following lymphodepletion, Cohort 2 patients were treated with 1.17, 1.14, and 1.15×10^9 transduced T-cells. Patients across cohorts have experienced cytopenias (up to Grade 4 neutropenia and thrombocytopenia) related to lymphodepleting chemotherapy followed by recovery. There were no reports of hepatic toxicity, cytokine release syndrome or DLTs in these

cohorts with minimum follow-up of 4 weeks. Although there were no RECIST-defined responses, 1 patient in Cohort 2 had a reduction in the size of 2 target lesions (1 mediastinal lymph node metastasis decreased by 42% at Week 24). Transient decreases in serum AFP levels post-ADP-A2AFP therapy were also observed. A digital PCR-based assay specifically targeting the packaging signal element of the lentiviral vector detected the presence of SPEAR T-cells in post-treatment tumor tissue from a patient in Cohort 1.
Conclusion: ADP-A2AFP T-cells have shown no evidence of on target or off target toxicity in the first 5 patients with transduced cell doses up to 1.17×10^9 cells. No protocol-defined DLTs were reported. Current data support continued investigation of ADP-A2AFP in Cohort 3 with target transduced cell doses 5×10^9 cells (range 1.2 to 6.0×10^9).

SAT514

A nationwide multicenter study of Japanese patients with unresectable hepatocellular carcinoma treated with regorafenib in real-world practice

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Background and Aims: Regorafenib was approved in Japanese patients with unresectable HCC (u-HCC) in Jun 2017. We performed a nationwide multicenter study of regorafenib therapy and investigated the factors associated with overall survival (OS).
Method: A total of 81 u-HCC patients received regorafenib from Jun 2017 at 12 sites in Japan were registered. Tumour assessments in accordance with modified RECIST was done using dynamic CT or MRI within 4–8 weeks and every 6–8 weeks thereafter. Adverse events (AEs) were graded according to the CTCAE ver4.0.
Results: Median age and body weight were 70 years and 59 kg. The baseline liver function was Child-Pugh class A in 70 (86%) patients and 50 (62%) patients were BCLC stage C. Median overall survival (OS) and follow-up duration were 14.1 and 8.5 months. Median overall time under treatment was 3.1 months. Median progression free survival (PFS) was 4.2 months. Based on mRECIST, CR was shown in 0 (0%), PR in 8 (13%), SD in 34 (53%), and PD in 21 (33%) patients. Overall response rate (ORR) and disease control rate (DCR) were 13% and 67%. Fifteen patients started regorafenib at the standard initial dose (160 mg/day) and 66 patients started at reduced doses. There were no significant differences in median OS and PFS between the standard and reduced group. The patients who experienced hand-foot skin reaction (HFSR) during regorafenib significantly showed better OS and PFS (<0.0001) than the patients without HFSR. The independent factors associated with OS in regorafenib therapy were pretreatment performance status (HR 3.5, 95%CI 1.42–8.64, p = 0.007), pretreatment Alb level (HR4.4 , 95%CI 1.82–11.8, p = 0.001), Major portal invasion (HR 10.4, 95%CI 2.94–37.2, p = 0.0003), and HFSR during regorafenib (HR 0.13, 95%CI 0.05–0.33, p < 0.0001). In the geriatric patients (≥75 years, n = 31), median OS and PFS were 8.4 and 3.1 months. In the geriatric patients with ALBI grade 1 or 2a (n = 10), the median OS was 12.7 months and no grade 3 adverse event associated with regorafenib therapy was reported.
Conclusion: Clinical outcome of regorafenib therapy for Japanese patients with u-HCC in real world practice was similar to the phase 3 clinical trial, even though the Japanese patients were older and had lower bodyweight. The geriatric patients with well-preserved liver function could tolerate regorafenib therapy and showed excellent survival.

SAT515

Antiplatelet therapy improves the prognosis of patients with hepatocellular carcinoma

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Background and Aims: Aspirin is demonstrated reducing the risk of colorectal cancer. In contrast, study of antiplatelet therapy for liver disease is limited. Antiplatelet therapy decreases the progression of hepatic fibrosis and prevents the development of hepatocellular carcinoma (HCC). However, effect of antiplatelet therapy after hepatocarcinogenesis remains unclear. This study aimed to clarify the effect of antiplatelet therapy for HCC patients.
Method: 697 consecutive naïve HCC patients, treated from January 2005 to May 2018, participated in this retrospective study. 104 patients used antiplatelet agents, aspirin or clopidogrel. We analyzed liver related death and periods to HCC progression, decompensated cirrhosis and bleeding with or without antiplatelet therapy. Kaplan-Meier method with log rank test was used to analyze the occurrence of events and the Cox proportional hazard model was used for multivariate analysis.
Results: Patients with antiplatelet therapy were older, and they had significant better liver function at the first treatment. Stage, tumor size and number, tumor markers were not different between patients with and without antiplatelet therapy. Patients with antiplatelet therapy had better prognosis than non-users (62.8% vs 37.4% / 5years, P < 0.005), and antiplatelet therapy was an independent factor to predict the prognosis by multivariate analysis (HR:0.5, 95%CI:0.4–0.7, P < 0.001). Recurrence after curative therapy (liver resection or radiofrequency ablation) was not different. However, time to HCC recurrence of patients received transcatheter chemoembolization as the first treatment was longer in patients with antiplatelet therapy (P < 0.05). Time to progress to decompensated cirrhosis was longer in patients with antiplatelet therapy (P < 0.01). Bleeding rate was not significantly different between the two groups.
Conclusion: Antiplatelet therapy reduced the risk of liver related death by anti-tumor effect and preservation of good hepatic reserve.

SAT516

No risk of hepatitis B reactivation in hepatocellular carcinoma patients with HBV-DNA >100 iu/ml undergoing immune checkpoint inhibitor immunotherapy by pre-emptive strategy

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Background and Aims: Immunotherapy with checkpoint inhibitor (ICI) is a promising and FDA-approved treatment for unresectable hepatocellular carcinoma (HCC). According to the clinical trials (CheckMate-040 and Keynote-224), effective anti-viral treatment and lower HBV viral load (<100 IU/mL) was required in patients with chronic hepatitis B before entering to ICI treatment. However, the rationale was still unclear.

Method: From May 2017, 66 patients had received treatment of ICI (nivolumab or pembrolizumab) for unresectable HBV related HCC in Taipei Veterans General Hospital. Among them, 62 patients with documented baseline serum HBV-DNA level were enrolled for clinical assessment. HBV reactivation is defined as a 10-fold increase in HBV viral load.
Results: At the date of data cut on November 15, 2019, the objective response rate was 27.8%, including 2 (3.7%) complete responses and 13 (24.1%) partial responses. The median time to response was 61 days (IQR 46–75 days), and the median duration of response was 5.8 months (IQR 2.9–10.0) for responders. Patients received nucleos(t)ide analogues (NUCs) (n = 55) had similar objective response rate (ORR) to those without NUCs treatment (n = 7) (ORR: 27.1% vs. 33.3%, p = 1.000). HBV reactivation developed in one patient (14.3%) who did not receive NUCs treatment during immunotherapy; whereas, no such event developed in patients with NUCs treatment. Among 23 patients with HBV viral load ≥100 IU/mL at the time of immunotherapy, 19 patients received pre-emptive NUCs treatment and 4 patients did not have NUCs treatment. All patients administrated with NUCs were safe from viral reactivation; whereas, one patient (25.0%) without NUCs treatment experienced HBV reactivation. The other patients with HBV viral load less than 100 IU/mL at the time of immunotherapy were free from HBV reactivation during immunotherapy regardless of NUCs treatment or not.
Conclusion: ICI treatment is not contraindicated for HCC patients with HBV viral load higher than 100 IU/mL once pre-emptive NUCs could be provided.

SAT517
Effect of antibiotics, proton pump inhibitors and steroids on survival and response to immune-checkpoint inhibitors in patients with hepatocellular carcinoma

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Background and Aims: Immune-checkpoint inhibitors (ICIs) are promising therapeutic agents for unresectable hepatocellular carcinoma (HCC). Prior exposures to antibiotics or other drugs were reported to have influences on the treatment response and survival in ICI-treated patients across malignancies. However, such probable effects were still unclear in HCC.
Method: From May 2017, 105 patients had received ICI treatment for unresectable HCC in Taipei Veterans General Hospital. Among them, 94 patients with evaluable radiographic images following treatment before November 15, 2019 were enrolled for clinical assessment. The effects of various drug exposures on treatment outcome were investigated.
Results: At the date of data cut, the objective response rate (ORR) was 25.5% including 6 (6.4%) complete responses and 18 (19.1%) partial responses. The median time to response was 63 days (IQR 50–75 days), and the median duration of response was 6.5 months (IQR 3.8–13.8) for responders. The median overall survival (OS) was 11.9 months (95% C.I. 5.3–18.5). Within 30 days prior to ICI treatment, 19 (20.2%), 30 (31.9%), and 3 (3.2%) patients had been administrated with antibiotics, proton pump inhibitors (PPIs), and steroid, respectively. Patients who were exposed to antibiotics before immunotherapy had similar ORR (21.1% vs. 26.7%, $p = 0.772$) but shorter overall survival (OS: 13.5 vs. 6.9 months, $p = 0.147$) than the others without antibiotic exposure. Besides, there was no significant differences about ORR (23.3% vs. 26.6%, $p = 0.738$) and OS (13.5 vs. 11.9 months, p = 0.948) according to the prior administration of PPIs. On the other hand, prior steroid treatment was associated with less ORR (0% vs. 26.4%, $p = 0.568$) and significantly shorter OS (2.6 vs. 12.5 months, $p = 0.004$) compared to the others without steroid treatment.
Conclusion: Prior administration with antibiotics, proton pump inhibitors and steroids before ICI therapy did not contribute to significant adverse effects on the treatment outcomes of unresectable HCC. However, poorer survival were observed in patients who had received steroids prior to ICI treatment.

SAT518
Nucleos(t)ide analogs reduces hepatocellular carcinoma mortality in patients with low HBV-DNA levels

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Background and Aims: Despite antiviral treatment has been shown to reduce hepatocellular carcinoma (HCC) mortality for hepatitis B virus (HBV)-related HCC in patients with high HBV-DNA levels, it is still unclear whether antiviral therapy is useful in reducing mortality in patients with low HBV-DNA levels.
Method: A retrospective analysis was performed of 853 patients diagnosed with HBV-related HCC with HBV-DNA <500 IU/mL between January 2008 and June 2017 at the Beijing Ditan Hospital. Patients were divided into antiviral group and non-antiviral group according to whether they were treated with Nucleos(t)ide Analogs (NA) in the first diagnosis of primary liver cancer in our hospital. We used 1:4 frequency matching by tumor size and Barcelona Clinic Liver Cancer staging to compare the antiviral group (n = 444) and non-antiviral group (n = 111). A Cox multivariate regression analysis was employed to evaluate the effects of NA therapy on the HR value and Kaplan-Meier survival curve for mortality risk in HCC patients. A log-

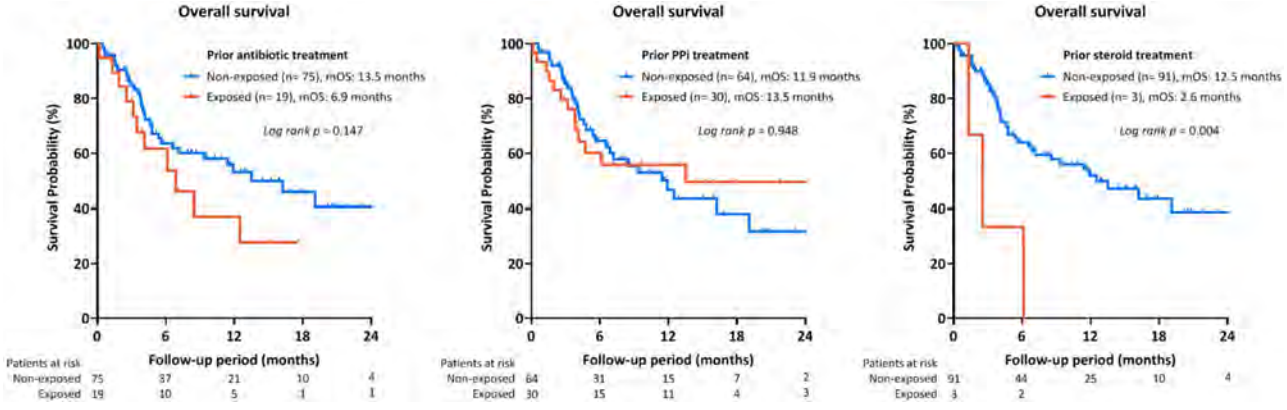

Figure: (abstract: SAT517)

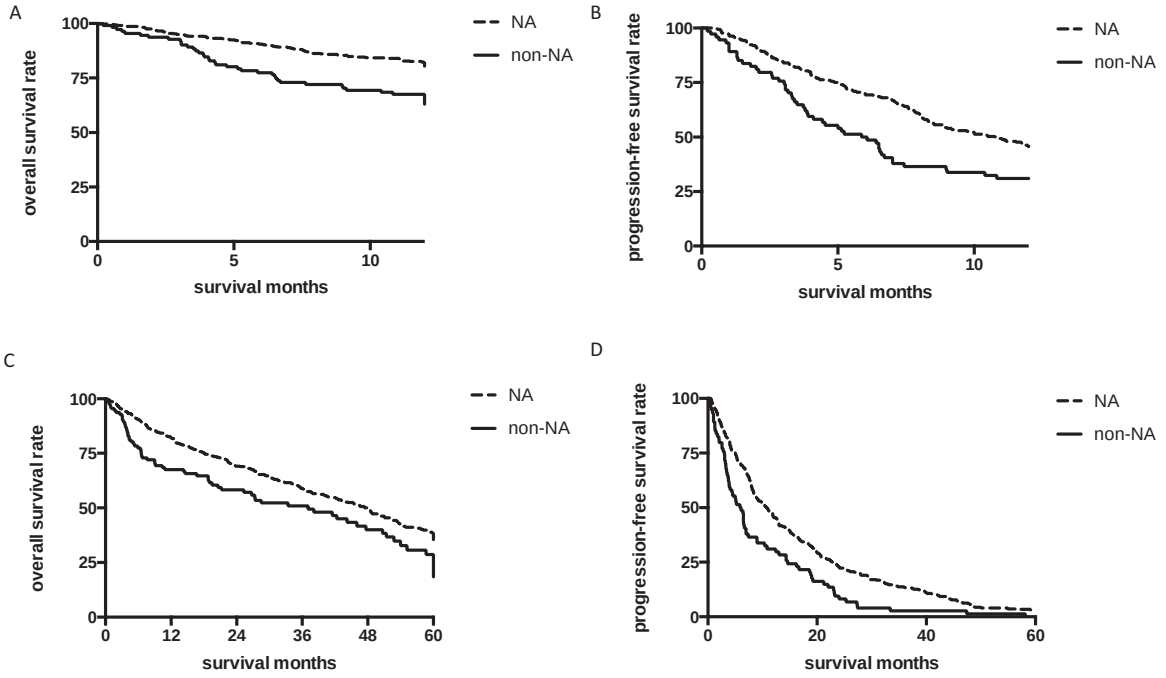

Fig. 1: (abstract: SAT518): Kaplan–Meier curves of overall survival (OS) and progression-free survival (PFS) for total 853 of propensity-score- matched patients. (A) OS and (B) PFS for 1 year; (C) OS and (D) PFS for 5 years.

rank test was performed to analyze the effect of NA therapy on the survival time of HCC patients.

Results: After propensity score matching, the 1-, 3-, and 5-year overall survival rates for the antiviral group and the control group were 78.8%, 61.9%, 26.2%, and 63.1%, 49.5%, and 12.9%, respectively. The l year progress free survival rates for the 2 groups were 63.3% and 54.1%, respectively. The overall survival for the antiviral group were significantly better than the control group (P = 0.001, P = 0.023, P = 0.018, respectively). There was no difference between the 1-year progression-free survival of the antiviral group and the non-antiviral group (P = 0.081). After adjusting for confounding prognostic factors in a Cox model, the relative risks of death for antiviral treatment was 0.651 [95% confidence interval (CI), 0.496– 0.856; P = 0.005]. Antiviral therapy was an independent protective factor of mortality.

Table 1: Univariate and multivariate Cox analysis for 5 year OS of Hepatocellular Carcinoma in PS matched patients

		Univariate analysis			Multivariate analysis	
	P	HR	95%CI	P	AdjustHR	95%CI
Gender	0.993	1.001	[0.770 1.302]			
Age	0.036*	1.357	[1.020 1.807]			
HBeAg	0.362	0.925	[0.783 1.093]			
antiviral	0.007*	0.681	[0.521 0.891]	0.002*	0.651	[0.496 0.856]
rGGT	0.000*	1.788	[1.390 2.300]	0.000*	1.661	[1.305 2.115]
MELD	0.000*	1.762	[1.361 2.280]	0.000*	1.601	[1.253 2.046]
AFP	0.026*	1.371	[1.039 1.811]	0.032*	1.736	[1.332 2.261]
Tumor Size	0.001*	1.600	[1.220 2.100]	0.000*	1.908	[1.464 2.486]
BCLCgroup	0.000*	1.865	[1.426 2.440]	0.000*	1.851	[1.721 1.990]

Conclusion: In patients with low HBV-DNA levels, antiviral therapy significantly reduced HCC mortality.

SAT519

Comparative effectiveness of nivolumab versus regorafenib for hepatocellular carcinoma patients who experienced sorafenib failure

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Background and Aims: Several treatment options are now available for patients with hepatocellular carcinoma (HCC) who fail sorafenib treatment. We aimed to compare the effectiveness of regorafenib and nivolumab in those patients.

Method: Consecutive HCC patients who received regorafenib or nivolumab after sorafenib failure were included. Primary endpoint was overall survival (OS) and secondary endpoints were time to progression, tumor response rate, and adverse events. Inverse probability of treatment weighting (IPTW) using the propensity score was conducted to reduce treatment selection bias.

Results: Among 150 study patients, 102 patients received regorafenib and 48 patients received nivolumab. Median OS was 6.9 (95% confidence interval [CI], 3.0–10.8) months for regorafenib and 5.9 (95% CI, 3.7–8.1) months for nivolumab (p = 0.77 by log-rank test) (panel A). In the multivariable analysis, nivolumab was associated with prolonged OS (vs regorafenib: adjusted hazard ratio [aHR], 0.54; 95% CI, 0.30–0.96; p = 0.04). After IPTW, although there was no statistically significant difference between the groups, nivolumab

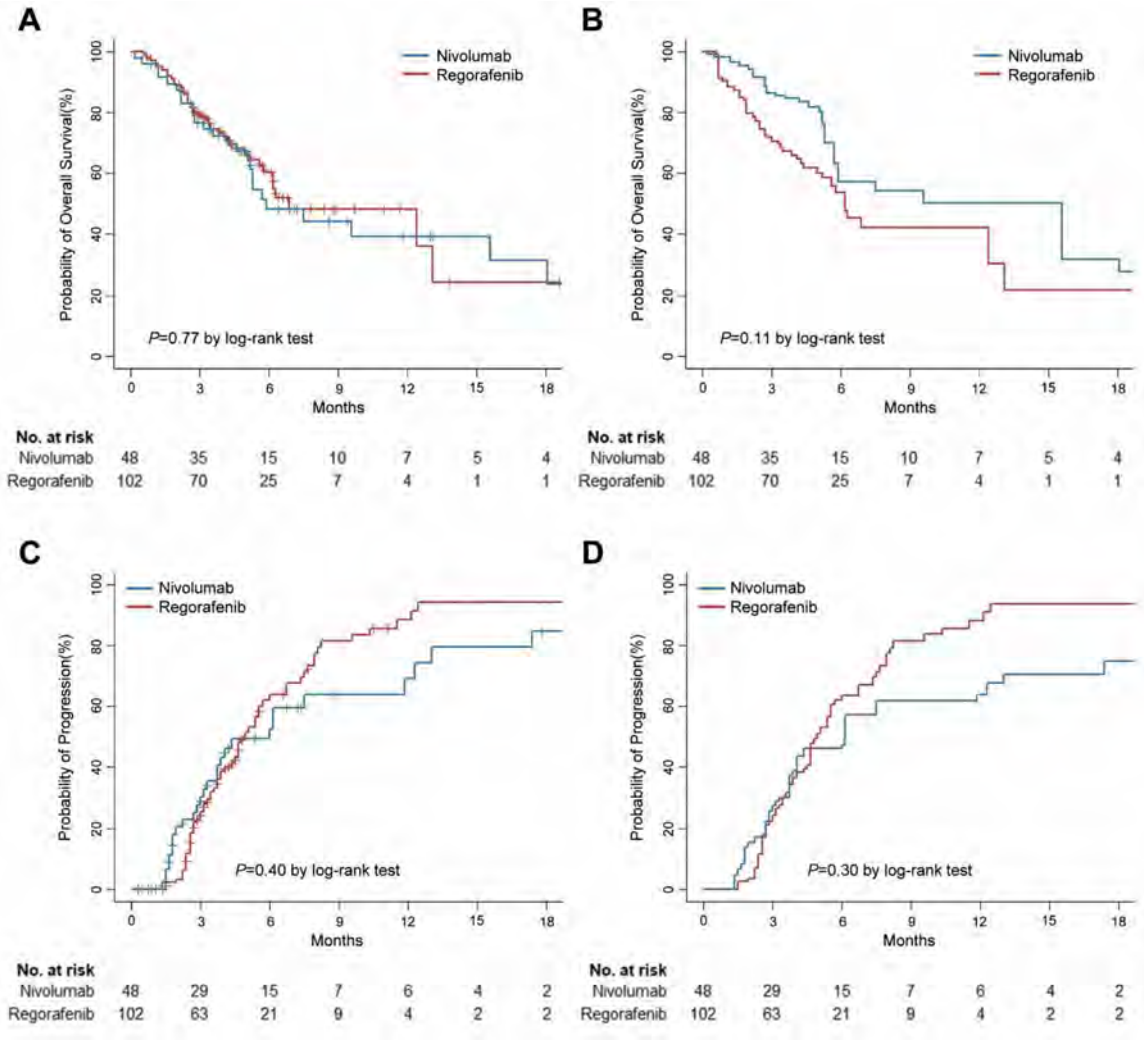

Figure: (abstract: SAT519)

was associated with better OS than regorafenib (p = 0.11 by log-rank test) (panel B). Weighted Cox proportional hazards model also revealed that the nivolumab treatment was associated with improved OS (vs regorafenib: aHR, 0.34; 95% CI, 0.18–0.65; p = 0.001). Time to progression was not significantly different between the groups (nivolumab vs regorafenib: aHR, 0.82; 95% CI, 0.51–1.30; p = 0.48) (panel C). Similar results were found after IPTW in the analysis for time to progression (panel D). Objective response rates were 5.9% and 16.7% in patients treated with regorafenib and nivolumab, respectively (p = 0.04).

Conclusion: After sorafenib failure, nivolumab was associated with improved OS and better objective response rate compared with regorafenib.

SAT520

Zinc phthalocyanine/sorafenib-conjugated bovine serum albumin nanoparticles provide effective synergistic therapy against hepatocellular carcinoma

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Background and Aims: Sorafenib, a multi-targeted kinase inhibitor, has been reported to exert a systemic benefit against advanced hepatocellular carcinoma (HCC). However, various side effects, such as hand-foot syndrome and perforating folliculitis, has been reported. Therefore, new approaches are urgently needed to improve the therapeutic effectiveness of sorafenib and to reduce its side effect. To overcome this limitation, we developed a Zinc phthalocyanine (ZnPc) and sorafenib (SFB) conjugated bovine serum albumin (BSA) to trigger photodynamic therapy (PDT), photothermal therapy (PTT), and chemotherapy, and investigated its effects in mice with HCC.

Method: For in vitro study, cell phenotype was determined with flow cytometry, cell counting kit 8, live and dead viability staining, colony formation, wound healing and Transwell assays. Apoptosis- and proliferation-related protein expression was analyzed using immunoblot. Reactive oxygen species (ROS) were detected using a luminescent assay. For in vivo study, human HCC cells were inoculated to form subcutaneous tumors, and were then implanted into the liver to establish orthotopic tumor models of HCC in nude mice. After tumors formed, mice were given an injection of ZnPc plus laser treatment, ZnPc-SFB@BSA plus laser treatment, BSA, sorafenib or vehicle via tail vein every other day for 2 weeks. Tumor growth and volume were monitored. Apoptosis- and proliferation-related protein expression was also analyzed using immunohistochemistry and immunoblot.

Results: After irradiation by a 730 nm laser, ZnPc-SFB@BSA nanoparticles significantly suppressed proliferation and metastasis, and

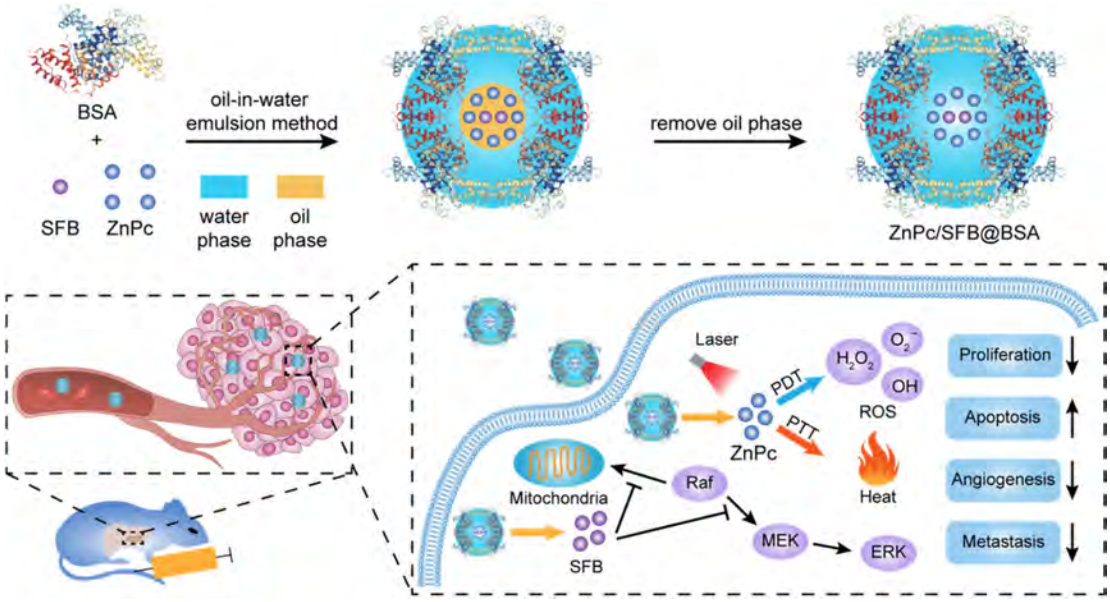

Figure: (abstract: SAT520)

promoted apoptosis *in vitro*. For in vivo study, combination therapy of Injection of ZnPc-SFB@BSA plus laser treatment slowed tumor growth by reducing tumor cell proliferation and the expression of MCL-1, Bcl-xl and Bcl-2, and by increasing tumor cell apoptosis, compared with other groups. More importantly, ZnPc-SFB@BSA nanoparticles presented low toxicity and excellent blood compatibility.

Conclusion: a multimodal therapy using combination of ZnPc with sorafenib via BSA nanoparticles can markedly suppress HCC growth and metastasis, representing a promising strategy for HCC patients.

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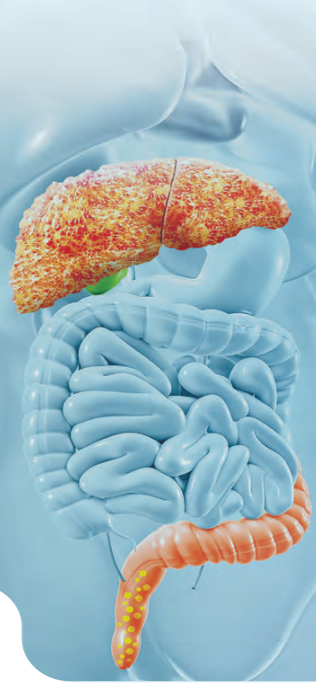

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will investigate the human microbiome to identify predictors and mechanisms associated with the development of decompensation of cirrhosis and progression to **acute-on-chronic liver failure (ACLF) and death.**

- → New microbiome-based tests for better stratification of cirrhosis patients
- → Personalized prediction and prevention of decompensation and ACLF
- → Clinical trial to predict response to treatment
- → Modern, effective nanobiosensors as clinical tools with improved specificity
- → More personalized treatment
- → Increased survival times
- → Decreased costs for the health systems

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